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(54) Title: INHIBITORS OF HIV MEMBRANE FUSION

(57) Abstract

Inhibitors of HIV membrane fusion and a method of identifying drugs or agents which inhibit binding of the N–helix coiled–coil and the C helix of HIV gp41 envelope protein.

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INHIBITORS OF HIV MEMBRANE FUSION

RELATED APPLICATIONS

This application is related to U.S. Provisional Application 60/043,280, entitled Core Structure of gp41 from the HIV Envelope Glycoprotein, by David C. Chan, Deborah Fass, Min Lu, James M. Berger and Peter S. Kim, filed April 17, 1997 and U.S. Application 09/062,241, entitled Core Structure of gp41 from the HIV Envelope Glycoprotein, by David C. Chan, Deborah Fass, Min Lu, James M. Berger and Peter S. Kim, filed April 17, 1998. The present application claims the benefit of U.S. Provisional Application 60/094,676, entitled Inhibitors of HIV Membrane Fusion by David C. Chan, Debra M. Ehrgott and Peter S. Kim, filed July 30, 1998; U.S. Provisional Application 60/100,265, entitled Inhibitors of HIV Membrane Fusion, by David C. Chan, Debra M. Ehrgott and Peter S. Kim, filed September 14, 1998 and U.S. Provisional Application 60/101,058, entitled Inhibitors of HIV Membrane Fusion, by David C. Chan, Debra M. Ehrgott and Peter S. Kim, filed September 18, 1998; and U.S. Provisional Application 60/132,295, entitled Inhibitors of HIV Membrane Fusion, by Debra M. Ehrgott, David C. Chan, Vladimir Malashkevich and Peter S. Kim, filed May 3, 1999. The entire teachings of these referenced applications are incorporated herein by reference.

GOVERNMENT SUPPORT

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BACKGROUND OF THE INVENTION

Structural studies of proteins from human immunodeficiency virus type 1 (HIV-1) have been essential in the development of anti-retroviral drugs. Structure-based drug development has been most intense for reverse transcriptase inhibitors and protease inhibitors, the two classes of HIV-1 drugs in clinical use. It would also be useful to be able to carry out structure-based drug development against HIV entry.

SUMMARY OF THE INVENTION

As described herein, the cavities on the surface of the N-helix coiled-coil of HIV envelope protein gp41 subunit (e.g., HIV-1 envelope protein gp41-subunit) are targets for drugs or other agents which, by binding the coiled-coil surface, particularly the cavities, inhibit HIV entry into cells. This is useful as the basis for identifying and designing drugs or agents which inhibit entry of HIV (e.g., HIV-1, HIV-2) into cells.

Results described herein show that the coiled-coil cavity (also referred to as the hydrophobic pocket) in the gp41 core is an attractive drug target and that molecules which bind the cavity interfere with (inhibit) HIV infectivity (HIV entry into cells). Applicants have shown, for the first time, that conserved residues projecting into the hydrophobic pocket clearly play a major role in the ability of C34 to inhibit HIV-1 infection. The importance of cavity contacts (between the N-helix coiled-coil cavity and residues of the C peptide region of gp41) to gp41 function is clear. Conversely, the importance of preventing such cavity contacts in inhibiting gp41 function and, thus, inhibiting HIV-1 entry into cells, is also clear. In addition, directing drugs against the hydrophobic pocket of the central-coiled coil of gp41 targets one of the most highly conserved regions of the HIV-1 envelope proteins, which means that drugs which target the coiled-coil surface, and particularly its hydrophobic pocket, will have broad activity against diverse HIV isolates and that it will be difficult for drug-escape mutants to emerge.

A variety of methods, such as mirror-image phage display techniques (T. N. Schumacher, *et al., Science, 271*:1854 (1996)), combinatorial chemistry (A. Borchardt, S. D. Liberles, S. R. Biggar, G.R. Crabtree, S.L. Schreiber, *Chem. Biol., 4*:961 (1997); J.C. Chabala, *Curr. Opin. Biotechnol., 6*:632 (1995)), rational drug design and other drug screening and medicinal chemistry methods can be used to identify D-peptides, peptidomimetics and small molecules that bind the coiled-coil cavity with sufficient affinity to inhibit HIV-1 infection. The close correlation between N36/C34 stability and C34 potency, described herein, suggests that the effectiveness of such compounds will depend critically on the strength of their cavity-contacts. As described herein, candidate compounds can be tested for their

ability to interfere with formation of a stable complex between C34 and N36 or their ability to disrupt binding of the two (disrupt the complex), thereby providing rapid, quantitative screens to identify and evaluate potential inhibitors of HIV-1 entry.

Alternatively, screening can be carried out to identify molecules or compounds which interfere with or disrupt binding of the N-helix coiled-coil cavity and a peptide which binds the cavity, thus providing methods of identifying molecules which are "pocket specific" binding agents or drugs. Molecules and compounds described herein (also referred to as drugs or agents) are useful to inactivate gp41 and, thus, prevent or reduce (inhibit) HIV-1 entry into cells. Without wishing to be bound by theory, it is reasonable to propose that these inhibitors bind to the pre-hairpin intermediate of gp41 and prevent its conversion to the trimeric hairpin structure of the gp41 core which corresponds to the fusion-active state of gp41. (Chan, D.C. and P.S. Kim, *Cell, 93:*681 (1998), See Figure 1). Thus, the present methods are useful to identify drugs or agents which inhibit (totally or partially) formation of the fusion-active state of HIV-1 gp41 envelope protein. In the method, the ability of a candidate inhibitor (also referred to as a candidate drug), which can be any type of compound or molecule, such as a small molecule (e.g., a small organic molecule), a peptide (a D-peptide or an L-peptide), a peptidomimetic, a protein or an antibody, to bind the N-helix coiled-coil of gp41 and form a stable complex is assessed. Compounds or molecules which bind to the N-helix coiled-coil are further assessed for their ability to inhibit gp41 function (inhibit membrane fusion), such as through HIV-1 infection (viral entry) and syncytium assays, representative models of which are described and referenced herein. Those agents shown to inhibit gp41 function through such assays can be further assessed for their activity in additional *in vitro* assays and in appropriate animal models (e.g., Letvin, N.L., *Science, 280*, (5371): 1875 - 1880 (1998), Hirsch, V.M. and P.R. Johnson, *Virus Research, 32* (2): 183-203 (1994); Reimann, K.A. *et al., J. Vivol., 70* (10): 6922-6928 (1996)). Any suitable approach can be used to assess binding of candidate inhibitors to the N-helix coiled-coil and, as a result of the work described herein, to the N-helix coiled coil cavity. In one embodiment, the ability of a candidate inhibitor to bind the synthetic peptide N36 (described in Lu, M. *et al., J.*

Biomol. Struct. Dyn. 15: 465 (1997), Chan, D.C. *et al., Cell, 89*, 263 (1997) and U.S. Provisional Application 60/043,280, entitled Core Structure of gp41 From the HIV Envelope Glycoprotein, by David C. Chan, Deborah Fass, Min Lu, James M. Berger and Peter S. Kim, filed April 17, 1997) is assessed. The stability of the resulting complexes is assessed using methods described herein.

In a particular embodiment of the method of identifying compounds or molecules (drugs or agents) which bind the N-helix coiled-coil cavity, a soluble model that presents the gp41 coiled-coil cavity is used. The six helix bundle of HIV gp41 consists of an internal trimeric coiled-coil, composed of three identical N-peptides, surrounded by three C-peptides which fit into a conserved hydrophobic groove on the outside of the trimeric coiled-coil. The C-terminal end of the trimeric coiled-coil contains a large cavity into which bulky hydrophobic groups from the C-peptide pack. This hydrophobic pocket is used as the target for anti-HIV drug discovery and/or design. Unfortunately, in the absence of the C-peptide, the N-peptide is aggregated and not 100% helical. Thus, simply using an N peptide from HIV-1 gp41, such as N36, N51 (Lu, M. *et al., Nature Struct. Biology*, 1995) or DP-107 (Wild *et al., PNAS 89:*10537-10541 (1992) is unlikely to provide an effective model for the N-helix coiled-coil.

As described herein, Applicants have succeeded in producing a soluble, non-aggregating trimeric peptide model of the hydrophobic pocket of HIV gp41 and, thus, for the first time, have provided a model that properly presents this hydrophobic pocket or cavity (in a manner or configuration which forms a similar structure to the corresponding residues in the HIV gp41 structure). (The terms "pocket" and "cavity" are used interchangeably.) As described, a peptide (also referred to as a fusion protein) which includes a soluble, trimeric coiled coil portion and a portion from the N-peptide region of HIV gp41 that includes the amino acid residues which form the pocket or cavity of the N-helix coiled-coil of HIVgp41 (the pocket-comprising residues of the N-peptide) has been produced and shown to be such a soluble model, useful to identify molecules or compounds which inhibit HIV gp41 function and, thus, HIV entry into cells. The trimeric version of the coiled-coil in the peptide (also referred to as a fusion protein) can be the coiled-coil region of a

protein which is not a protein of HIV (a non HIV protein, such as GCN4-pI$_Q$I) or a protein of HIV origin (a protein derived from HIV or having the same or a similar amino acid sequence as an HIV protein). In a specific embodiment, the soluble, non-aggregating trimeric peptide model of the large cavity, referred to as IQN17, comprises a trimeric version of the coiled-coil region of GCN4, the yeast transcription activator, and a portion of the C-terminal end of the N peptide of gp41. IQN17 contains 29 residues of GCN4-pI$_Q$I (formerly referred to as GCN4-pIQ in U.S. Provisional Application 60/101,058) (Eckert, D.M. et al. *J. Mol. Biol., 284:*859-865 (1998)), including three mutations for increased solubility, and 17 residues of HIV; there is a one residue overlap between the two proteins, making the total length of the fusion protein 45 residues. The sequence of GCN4-pI$_Q$I is: ac-RMKQIEDKIEEI LSKQYHIENEIAR IKKLIGER (SEQ ID NO:1). The HIV Sequence is: LLQLTVWG IKQLQARIL (SEQ ID NO:20). The sequence of IQN17 is: ac-RMKQIEDKIEEIESKQKKIENEIARIKK LLQLTVWGIKQLQARIL-am (SEQ ID No:2). The HIV portion is underlined in SEQ ID No: 2; ac- represents an N-terminal acetyl group and -am represents a C-terminal amide. The sequence of the soluble, trimeric version of the coiled-coil region of GCN4 (referred to as a soluble, trimeric coiled coil of GCN4) in IQN17 is: RMKQIEDKIEEIESKQKKIENEIARIKK (SEQ ID No: 25). The superhelix parameters such as rise and pitch (Harbury, P.B. *et al., Nature 371*:80-83 (1994); Harbury *et al., PNAS 92*:8408-8412 (1995)) of the GCN4-pI$_Q$I coiled coil are nearly identical to the HIV gp41 N-helix coiled coil. Therefore, the resulting fusion protein molecule (IQN17) is predicted to form a long trimeric coiled coil, which presents the N-peptide hydrophobic cavity at the C terminus. IQN17 is fully helical, as determined by circular dichroism, with a molar ellipicity at 222nm of -36,000 deg cm^2 $dmol^{-1}$. As determined by sedimentation equilibrium, IQN17 is close to a discrete trimeric species with a ratio of observed molecular weight to calculated molecular weight ranging from 3.00 to 3.16 times the monomer molecular weight at a concentration of 20 μM. As determined by X-ray crystallography, IQN17 presents the N-peptide hydrophobic pocket in a manner that is nearly identical to the pocket in the HIV gp41 N-helix coiled coil.

The IQN17 molecule (in the natural L-handedness or enantiomeric D-handedness) can be used in screens, including high-throughput drug screens, to identify molecules that bind to the coiled-coil pocket. The IQN17 molecule, in the D-handedness, has been used as a target in mirror image phage display (Schumacher *et al., Science, 271: 1854,* 1996) to identify small molecules (D-peptides) which bind to the hydrophobic pocket of gp41 (in the natural L-handedness) and inhibit HIV-membrane fusion. The desired target (the N-helix of HIV gp41 which includes the hydrophobic pocket) is the exact mirror image of the naturally-occurring target. It is used to screen a library or collection of compounds or molecules which are to be assessed for their ability to bind the mirror image of the naturally-ocurring coiled-coil pocket. The mirror image of a compound or molecule found to bind the mirror image of the naturally-occurring gp41 pocket, will bind the gp41 pocket in the natural handedness. The library or collection screened can be of any type, such as a phage display library, peptide library, DNA library, RNA library, combinatorial library, collection of chemical agents or drugs, cell lysate, cell culture medium or supernatant containing products produced by cells. In the case of a phage display library, the D-target is used to screen phage coat proteins. Specific phage clones that bind to the target are identified and the mirror images of the expressed proteins are chemically synthesized with D-amino acids. By using IQN17 in mirror-image phage display, D-peptides that bind to the gp41 hydrophobic pocket have been identified. Further assessment has been carried out, as described, to demonstrate the ability of D-peptides to inhibit HIV gp41 function. D-peptides which bind the gp41 hydrophobic pocket and inhibit HIV infectivity have been identified. D-peptides which bind the hydrophobic pocket also will serve as lead molecules for drug development and/or reagents for drug discovery (where the drugs bind to the coiled-coil pocket and inhibit HIV infectivity). The IQN17 molecule, in the natural L-handedness, can be used in screens, including high-throughput screens, to identify molecules that bind to the coiled-coil pocket. IQN17 can be used to screen a collection or library of compounds or molecules which are to be assessed for their ability to bind the hydrophobic pocket. The library or collection screened can be of any type, such as a phage display library, RNA library, DNA library, peptide library,

combinatorial library, collection of chemical agents or drugs, cell lysate, cell culture medium or supernatant containing products produced by cells. Compounds or molecules which bind the hydrophobic pocket also will serve as lead molecules for drug development and/or reagents for drug discovery.

Fusion proteins which are variants of IQN17 can be produced and used to screen for drugs which bind the gp41 N-helix coiled-coil pocket. Any of a wide variety of variations can be made in the GCN4-pI$_Q$I component of IQN17 and used in the method, provided that these changes do not alter the trimeric state of the coiled-coil. For example, the amino acid composition of the GCN4 component can be changed by the addition, substitution, modification and/or deletion of one or more amino acid residues, provided that the trimeric state of the coiled-coil is maintained. For example, the Asp residue in IQN17 (at a "f-position" of the coiled coil) can be replaced by any of the naturally-occurring amino acids. (O'Neil and DeGrado, *Science 250*:646 (1990)). Alternatively, this component of the fusion protein can be a trimeric version of the coiled-coil region of another protein, such as that from Moloney Murine Leukemia Virus (Fass, D. *et al. Nature Struct. Biology, 3*:465 (1996)), GCN4-pII (Harbury *et al., Nature, 317*:80, 1994) or the ABC heterotrimer (Nautiyal and Alber, *Protein Science 8*:84 (1999)).

Changes can also be made in the amino acid composition of the fusion protein component which is the C-terminal portion of the HIV gp41 N peptide to produce IQN17 variants. The C-terminal portion can be changed by the addition, substitution, modification and/or deletion of one or more amino acid residues. The amino acid composition of either or both components of the fusion protein can be altered, and there is no limit to the number or types of amino acid residue changes possible, provided that the trimeric state of the coiled-coil and the hydrophobic pocket of the N peptide of HIV gp41 are maintained. IQN17, IQN17 variants or any soluble model of the large cavity can be used to screen for drugs which bind the N-helix coiled-coil, especially the pocket, or for lead drug candidates or candidates for use in vaccine preparations, to be further screened using methods known to those of skill in the art, such as in a high throughput format.

Results described herein are useful to screen for inhibitors of HIV gp41

which are variants of C34 as described below. Once a variant of C34, such as a C34 variant which stably binds N36, has been identified, it can be used and further assessed as obtained or it can be modified (e.g., by altering, adding, deleting or substituting at least one amino acid residue or adding a non-amino acid substituent), if desired or needed (e.g., to enhance stability, solubility, bioavailability). Alternatively, a C34 variant can be assessed to determine if a shorter component (region of fewer amino acid residues) also is active as an inhibitor. As discussed herein, the three C34 residues Trp^{628}, Trp^{631} and Ile^{635} that pack into the deep, conserved pocket in the N36 trimer are critical for inhibitory activity. The observation that C34 variants that have a higher affinity for the N36 coiled-coil have more potent inhibitory activity against HIV infection forms the basis for screens to identify and evaluate potential inhibitors. For example, using the "split-synthesis" technique (Chen, C.L., *et al. Methods Enzymol. 267:211-219 (1996)*; Lam, K.S. *et al.*, *Nature*, *354*: 82-84, (1991)) of combinatorial peptide chemistry, a library of C34 variants is synthesized in which the three critical hydrophobic residues are randomly replaced by chemical substitutions of varying hydrophobic character. This synthesis technique results in the generation of a vast library of beads, each containing many copies of a single variant C34 peptide (i.e., a "one-bead, one-compound" type of library). To identify C34 variants which stably bind the N-helix coiled-coil, a labeled version of N36 (or a modified N-peptide) is mixed with the peptide beads under conditions (e.g., elevated temperature) that restrict binding to only those C34 variants with the highest affinity. Binding is measured by detection of the label on the N-helix peptide, using known methods. Simple modifications of the split-synthesis technique allow ready identification of the selected peptide sequence by mass spectroscopy (Youngquist, R.S. *et al.*, *J. Amer. Chem. Soc. 117*, 3900-3906 (1995)). The C34 variants selected, particularly those with the highest binding affinities for N36, are tested in syncytium and infection assays for gp41 inhibitory activity. Truncated versions of these C34 variants, containing only the cavity-binding region, can also be tested for inhibitory activity. Alternatively, a library of other peptides to be assessed can be synthesized to generate a library of beads, each containing (having bound thereto) a peptide to be assessed. This library

is analyzed as described above for the C34 variants and resulting hits (members with appropriate binding affinities for N36) are further analyzed for gp41 inhibitory activity. As a second example, the N36 peptide or the soluble variants described earlier, such as IQN17, GCN4-N-helix peptide can be used as a target for phage display or mirror-image phage display techniques to identify peptides that bind to the cavity.

IQN17 can also be used to raise antibodies (monoclonal and/or polyclonal) that bind to the coiled-coil cavity. IQN17 can further be used, either alone or in combination with other materials, in a vaccine, which will elicit the production of antibodies that bind to the coiled-coil in the individual to whom it is administered (the vaccinee), and thereby offer protection against infection and/or disease.

Peptides, both D-peptides and L-peptides, which fit into a deep hydrophobic pocket in the trimeric N-helix coiled-coil of HIV-1 envelope glycoprotein gp41 are also the subject of this invention. The D-peptides are the first molecules that have been shown to bind exclusively to the gp41 hydrophobic pocket. The observation that these D-peptides inhibit gp41-mediated membrane fusion processes (syncytia formation and viral infection) provides the first direct demonstration that HIV-1 infection can be inhibited by molecules that bind specifically to pocket. The validation of the gp41 hydrophobic pocket as a drug target sets the stage for the development of a new class of orally bioavailable anti-HIV drugs, that work by inhibiting viral entry into cells. Such drugs would be a useful addition to the current regimen used to treat HIV-1 infection with combination therapies. D-peptides, such as the D-peptides described herein, portions, modification and variants thereof and larger molecules (e.g., polypeptides) which comprise all or a portion of a D-peptide described herein, are useful to inhibit HIV membrane fusion and, thus, HIV entry into cells. D-peptides, corresponding to the D-amino acid version of phage sequences identified as described herein, are inhibitors of HIV-1 infection and syncytia formation. The C-terminal residues in these D-peptide inhibitors have the sequence pattern: CXXXXXEWXWLCAA-am. (In the phage-display library, the positions corresponding to the C residues were encoded as either C or S, the positions corresponding to the AA residues were encoded as such and the other 10

positions (indicated by X) were randomly encoded. The -am represents a C-terminal amide, added as part of the peptide synthesis procedure.) The N-terminal residues in the D-peptide inhibitors are, for example, ac-GA, ac-KKGA, or ac-KKKKGA. The ac- represents an N-terminal acetyl group added as part of the peptide synthesis procedure. The C-terminal amide and the N-terminal acetyl group are optional components of D-peptides of this invention. Other N-terminal residues can be included, in place of or in addition to those in the previous sentence, as desired (e.g., to increase solubility). For example, D-peptides of the following sequences are also the subject of this invention:

ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 28);
ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 29);
ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 30);
ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 31);
ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 32); and
ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 33).

The amino acid residues are represented by the single letter convention and X represents any amino acid residue (naturally occurring or non-naturally occurring) or other moiety, such as a modified amino acid residue.

Further, the ten amino acid residue "core" (the 10-mer which is flanked at each end by a cysteine residue) of the 12 amino acid residue peptide, as well as portions, modifications and variants of the 10-mers are also useful to inhibit membrane fusion and entry of HIV into cells. Variants, portions and modifications of these peptides are also useful as inhibitors. As described further herein, D-peptides which comprise a consensus sequence (e.g., WXWL (SEQ ID NO: 23), EWXWL (SEQ ID NO: 24), CXXXXXEWXWLC (SEQ ID NO: 12) or a portion thereof) have been shown to bind the N-helix coiled-coil and are useful to inhibit membrane fusion and entry of HIV into cells. The enantiomeric peptides (D-peptides) do not serve as efficient substrates for enzymes, such as proteases and, therefore, are more resistant to proteolytic degradation than are L-peptides; they are also less immunogenic than are L-peptides.

Specific embodiments of D-peptides of the present invention are:

(a) CDLKAKEWFWLC (SEQ ID NO: 3);

(b) CEARHREWAWLC (SEQ ID NO: 4);

(c) CELLGWEWAWLC (SEQ ID NO: 5);

(d) CLLRAPEWGWLC (SEQ ID NO: 6);

(e) CSRSQPEWEWLC (SEQ ID NO: 7);

(f) CGLGQEEWFWLC (SEQ ID NO: 8);

(g) CMRGEWEWSWLC (SEQ ID NO: 9);

(h) CPPLNKEWAWLC (SEQ ID NO: 10);

(i) CVLKAKEWFWLC (SEQ ID NO: 11);

(j) KKGACGLGQEEWFWLC (SEQ ID NO: 15);

(k) KKGACELLGWEWAWLC (SEQ ID NO: 16);

(l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);

(m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);

(n) KKGACPPLNKEWAWLC (SEQ ID NO: 19);

(o) a D-peptide comprising WXWL (SEQ ID NO: 23);

(p) a D-peptide comprising EWXWL (SEQ ID NO: 24);

(q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)

(r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);

(r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);

(t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);

(u) ac-GACGLGQEEWFWLCAA-am (SEQ ID NO: 44);

(v) ac-KKGACGLGQEEWFWLCAA-am (SEQ ID NO: 15);

(w) ac-KKKKGACGLGQEEWFWLCAA-am (SEQ ID NO: 45)

(x) ac-GACDLKAKEWFWLCAA-am (SEQ ID NO: 35);

(y) ac-KKGACDLKAKEWFWLCAA-am (SEQ ID NO: 39);

(z) ac-KKKKGACDLKAKEWFWLCAA-am (SEQ ID NO: 46);

(a') ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);

(b') ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);

(c') ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);

(d') ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);

(e′) ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);

(f′) ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);

(g′) ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);

(h′) ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);

(i′) ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);

(j′) ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);

(k′) ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);

(l′) ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);

(m′) ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);

(n′) ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);

(o′) ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);

(p′) ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);

(q′) ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);

(r′) ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);

(s′) ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);

(t′) ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);

(u′) ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);

(v′) ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);

(w′) ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);

(x′) ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and

(y′) a variant of a sequence of (a) through (x′), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.

D-peptides described herein, which are ligands shown to bind the N-helix pocket, are also useful in drug screens to identify compounds or molecules (e.g., from chemical libraries, recombinantly produced products, naturally-occurring substances, culture media or supernatants) which bind the N-helix pocket and thus, are also inhibitors of HIV. For example, a competitive assay can be carried out by combining a D-peptide which binds the N-helix cavity (e.g., a D-peptide described herein); IQN17 (e.g., in the natural L-handedness), or another fusion protein which

is a soluble model that presents the N-helix cavity; and a candidate inhibitor (a compound or molecule to be assessed for its ability to bind the N-helix cavity). For example, D10pep5 or D10pep1, IQN17, and a candidate inhibitor (candidate drug) can be combined using buffer conditions and peptide concentrations appropriate for binding of D10pep5 or D10pep1 to IQN17. The extent to which binding of the D-peptide occurs is determined and compared to the extent to which binding occurs under the same conditions, but in the absence of a compound or molecule (referred to as a candidate drug or candidate inhibitor) to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 envelope protein (in a control). If binding of D10pep5 or D10pep1 occurs to a lesser extent in the presence of the candidate inhibitor (test sample) than in its absence (control sample), the candidate inhibitor is a ligand which binds the N-helix coiled-coil cavity and, thus, is an inhibitor. Inhibitors identified in this manner can be further assessed for their activity in viral infectivity assays and synctia formation assays, such as those described herein. Those inhibitors which show activity in such assays can be further assessed in an appropriate animal model or in humans.

Any method by which binding of the D-peptide, known to bind the N-helix cavity, can be detected can be used to assess whether the candidate inhibitor interferes with binding. For example, the D-peptide can be detectably labeled and the extent to which the label appears on the N-helix cavity (as a result of binding of the D-peptide) detected, in the presence and in the absence of the candidate inhibitor. If less label appears on the N-helix cavity of IQN17 (or other appropriate fusion protein) in the presence of the candidate inhibitor (in the test sample) than in its absence (in the control sample), then the candidate inhibitor is a ligand which binds the N-helix cavity (and interferes with binding of the D-peptide). Alternatively, the D-peptide (e.g., D10pep5 or D10pep1) and IQN17 can be labeled with a fluorophore (e.g., with EDANS; 5-(2'aminoethyl)aminonaphthalene-1-sulfonic acid) with an appropriate quencher that quenches the fluorescent signal of the fluorophore when it is in close proximity (e.g., DABCYL; 4-(4'-dimethylaminophenylazo)benzoic acid). If the candidate inhibitor binds the N-helix cavity of IQN17, fluorescence is observed, since, as a result of binding of the

candidate inhibitor, the D-peptide is not brought into sufficiently close proximity to the quencher to permit it to quench the reporter signal. Alternatively, the fluorescent reporter molecule can be on the IQN17 and an appropriate quencher on the D-peptide. In either case, the position of the reporter or quencher on IQN17 must be such that when the D-peptide binds the N-helix cavity, the reporter and quencher moieties are in sufficiently close proximity to each other that quenching occurs (Tyagi, S., *et al.*, *Nature Biotechnology 16*:49 (1998)).

Also the subject of this invention are drugs (compounds and molecules) which bind the N-helix coiled-coil pocket of HIV gp41 and inhibit (partially or totally) HIV entry into cells. In one embodiment, these drugs can be identified as described herein or by other methods. Drugs which bind the N-helix coiled-coil pocket of HIV gp41 are useful as therapeutic agents (to prevent HIV entry into cells or reduce the extent to which it occurs), as research tools (e.g., to study the mechanism of HIV gp41 function) and to assess the rate of viral clearance by an individual (e.g., in an animal model or an infected human).

Also the subject of this invention are compositions, useful in methods of interfering with entry of HIV into a mucosal cell; these compositions comprise an appropriate carrier or base and at least one component selected from the group consisting of:

(a) C34 peptide;

(b) DP178;

(c) T649;

(d) T1249;

(e) a derivative of (a) - (d);

(f) a D-peptide which binds to the hydrophobic pocket of HIV gp41;

(g) a derivative of (f);

(h) a combination of two or more of (a)-(g); and

(i) a molecule that inhibits HIV infectivity by binding to the N-helix coiled coil.

The compositions can comprise one such component or two or more components.

A further subject of this invention are compositions (e.g., proteins or

proteinaceous materials) that can be used to elicit an immune response (e.g., antibody production) that will protect (partially or totally) against HIV infection and/or disease. Such compositions are useful as protective agents (e.g., vaccines) and to obtain antibodies (monoclonal and/or polyclonal) that are useful as research tools, diagnostic tools, drug screening reagents, and to assess viral dynamics (rates of production and clearance of virus) in animal models or infected humans.

Also the subject of this invention is a list of atomic coordinates for the X-ray crystal structure of the complex between IQN17 and D10pep1. Also the subject of this invention is a list of coordinates for the X-ray crystal structure of IQN17. These coordinates can be used (e.g., as an electronic file for computer graphics programs) to create a model of the complex which indicates how D10pep1 binds to the N-helix coiled-coil cavity and models of the N-helix coiled-coil cavity. Such models can be used, in methods known to those of skill in the art such as in computer graphics modeling, to build new models to evaluate the likelihood of binding to the N-helix coiled-coil cavity by other peptides, peptidomimetics, small molecules, drugs or other compounds. Such models can also be used to build new models for the structures of molecules (peptides, peptidomimetics, small organic molecules, drugs or other compounds) that bind the N-helix coiled-coil cavity (e.g., H. Kubinyi, *Curr. Op. Drug Discov. Develop.*, *1*:16 (1998); P.L. Wood, *ibid, 1*:34 (1998); J.R. Morphy, *ibid. 1*:59 (1998)). These models and the corresponding lists of atomic coordinates can be used to identify, evaluate, discover and design more effective and/or new D-peptides, L-peptides, peptidomimetics, other small molecules or drugs that inhibit HIV infectivity, using methods known to those of skill in the art. A further subject of this invention is a method of producing or identifying a drug which fits (packs into, binds) the N-helix coiled-coil pocket of HIV gp41 through the use of atomic coordinates of a crystal, such as a crystal of a soluble, trimeric peptide model of the HIV gp41 hydrophobic pocket described herein (e.g., IQN17 or a variant thereof), a crystal of such a model in complex with a D-peptide (e.g., IQN17 or a variant thereof in complex with a D-peptide described herein, such as D10pep1) or a crystal of the N-peptide region of HIV gp41 comprising the amino acid residues which comprise the pocket of the N-helix coiled-coil of HIV gp41.

The method comprises obtaining a crystal of the soluble model, such as the empty soluble model (not in complex with a D-peptide), obtaining the atomic coordinates of the crystal (e.g., of the crystal of the empty soluble model, such as IQN17); using the atomic coordinates obtained to define the N-helix coiled-coil pocket of HIV gp41; identifying a molecule or compound which fits the N-helix coiled-coil pocket and obtaining the molecule or compound; contacting the molecule or compound with the N-helix coiled-coil pocket (e.g., by contacting it with a polypeptide which comprises the pocket (e.g., IQN17 or a variant thereof or the N-peptide) to assess (determine) the ability of the molecule or compound to fit the pocket of HIV gp41, wherein in the molecule or compound fits the pocket, it is a drug which fits the N-helix coiled-coil pocket, whereby a drug which fits the pocket is produced. The atomic coordinates of the crystal can be obtained by X-ray diffraction studies or form a computer file or Protein Data Base (PDB), such as the PDB presented herein for IQN17 (Figures 11A-11V).

Similarly, the method can be carried out using a crystal of a soluble trimeric model in complex with a D-peptide (e.g., a D-peptide described herein, such as D10pep1) or a crystal of the N-peptide region of HIV gp41 which comprises the pocket of the N-helix coiled coil.

Drugs produces in this manner can be further assessed to conform their ability to fit into the pocket (e.g., by NMR) and can be assessed for their ability to inhibit HIV entry into cells (e.g., by a syncytia assay or infectivity assay).

The teachings and entire contents of all documents cited herein are expressly incorporated by reference into this application.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic of HIV-1 gp41 showing the N36 (SGIVQQQNNLLRAIEQQHLLQLTVWGIKQLQARIL) (SEQ ID NO:13) and C34 (WMEWDREINNYTSLIHSLIEESQNQQEKNEQELL) (SEQ ID NO: 14) peptides located within two regions containing 4,3 hydrophobic heptad repeats (labeled heptad repeat 1 and heptad repeat 2, also referred to as N-peptide region and C-peptide region, respectively). The underlined residues in C34 were mutated in this

study. Three of these residues (W, W and I) project into the N36 cavity, whereas two of these residues (M and R) do not. FP, fusion peptide; S-S, disulfide bond; TM, transmembrane region; INTRA, intraviral region.

Figure 2 is a graph showing the correlation of C34 inhibitory potency with N36/C34 stability. C34 peptide variants containing substitutions at position Trp^{631} were tested for inhibition of viral entry (filled circles) and cell-cell fusion (open circles). IC_{50} values are plotted on a logarithmic scale against the $_{Tm}$ (melting temperature) of the corresponding N36/C34 complex. The identities and chemical structures of the substitutions are drawn under the corresponding data points. In order of increasing hydrophobic bulk, the substitutions were: glycine (Gly), alanine (Ala), L-α-aminobutyric acid (Abu), valine (Val), leucine (Leu), phenylalanine (Phe), the wildtype residue tryptophan (Trp), and L-β-(1-naphthyl) alanine (Nal). Error bars indicate the standard error from triplicate experiments.

Figure 3 shows the amino acid sequences of D-peptides (SEQ ID NOS: 34, 38, 15, 35, 16, 17, 36, 40, 41, 18 and 19) and the consensus sequence (SEQ ID NO.: 12). As represented, each peptide is flanked by GA on the N-terminus and AA on the C-terminus, and comprises a blocking group at the N-terminus: (Acetyl-GA-C-10mer-C-AA-$CONH_2$; this can also be represented as ac-GA-C-10mer-C-AA-am). The single letter conventions which are used to represent amino acid residues are as follows: G=glycine; A=alanine; C=cysteine; D=aspartic acid; L=leucine; K=lysine; E=glutamic acid; W=tryptophan; F=phenylalanine; R=arginine; H=histidine; S=serine; and Q=glutamine.

Figure 4 is a schematic representation of mirror-image phage display with the D-IQN17 target, in which: (1) rounds of phage selection are carried out to identify binders to D-IQN17; (2) individual clones are sequenced; (3) binding specificity is assessed by determining whether the phage bind to the gp41 region of D-IQN17; (4) D-peptides of those phage sequences which bind are produced; and (5) the anti-HIV activity of the D-peptides is assayed.

Figures 5A and 5B show the crystal structure of IQN17 bound to D10pep1. IQN17 is shown to be a continuous three-stranded coil, and binding of the conserved amino acid residues of D10pep1 is shown to be to the hydrophobic pocket of IQN17,

formed by the 17 residues derived from HIV gp41. Figure 5A shows IQN17, consisting of GCN4-pI$_Q$I residues fused to HIV-1 gp41 residues and the binding of D10pep1 to the hydrophobic pocket of IQN17 (area within box). The D-peptide which binds to the pocket is represented by the branched extensions (i.e., stick representation). Figure 5B is an enlargement of the area within the box and shows the conserved residues that pack into the pocket (Trp, Trp Leu) as well as a glutamic acid (Glu).

Figures 6A and 6B show results of syncytia assays, using the D-peptides described herein. Figure 6A is a graphic representation of results of syncytia assays. Figure 6B represents IC_{50} data for D-peptides, with results from one or more experiments.

Figures 7A-7N are the PDB file which lists the atomic coordinates for the crystal structure of D10pep1 bound to IQN17, in which residues 0-28 of the A chain are derived from the GCN4-pI$_Q$I sequence (with three mutations), residues 29-45 of the A chain are derived from the HIVgp41 sequence, residues 0-16 of the D chain represent the D-peptide, ordered water molecules are represented as W, and a bound chloride ion as chain I. Residue 0 represents the acetyl group. The PDB file represents a monomer; the trimer is formed by crystallographic symmetry.

Figures 8A and 8B show results of assessment of inhibition of HIV-1 membrane fusion by a D-peptide. Figure 8A shows results of syncytia assay with no D-peptide. Figure 8B shows results of syncytia assay with D-peptide.

Figures 9A-9C show results of ^{1}H NMR experiments characterizing the aromatic residues of IQN17/D-peptide complexes. Figure 9A shows 1D-NMR spectra of D10pep1a (top), IQN17 (middle) and a 1:1 complex of D10pep1a and IQN17 (bottom). The x-axis is the same as for (C) below. Upfield peaks assigned to the four scalar-coupled aromatic ring protons of Trp-571 are indicated. The unmarked upfield peak of the bottom trace corresponds to an unassigned Hα resonance. Figure 9B shows 1D spectra of 1:1 complexes between IQN17 and each D-peptide (as labeled). The same four protons are indicated in some spectra. Figure 9C shows a 2D-NMR TOCSY spectrum of IQN17/D10pep1a complex. Cross-peaks linking these four tryptophan protons are indicated, along with specific assignments.

The TOCSY mixing time was 42ms.

Figure 10 shows the conformation of the D10pep1 peptide as in the complex with IQN17, as determined by X-ray crystallography.

Figures 11A – 11V are the PDB file which lists the atomic coordinates for the crystal structure of IQN17, in which residues 0-28 of the A, B and C chains of the IQN17 trimer are derived from GCN4-pI_QI sequence (with three mutations), residues 29-45 of the chains A, B, and C are derived from HIV gp41, ordered water molecules are represented as W, and a bound chloride ion as chain I. The PDB file represents a whole trimer in the crystallographic asymmetric unit.

DETAILED DESCRIPTION OF THE INVENTION

The gp41 subunit of the HIV-1 envelope protein mediates fusion of viral and cellular membranes. The crystal structure of the gp41 ectodomain core is a six-helix bundle composed of three helical hairpins, each consisting of an N-helix paired with an antiparallel C-helix (D. C. Chan, D. Fass, J. M. Berger, P. S. Kim, *Cell, 89*:263 (1997),
W. Weissenhorn, A. Dessen, S.C. Harrison, J. J. Skehel, D. C. Wiley, *Nature, 387*:426 (1997); K. Tan, J. Liu, J. Wang, S. Shen, M. Lu, *Proc. Natl. Acad. Sci. USA, 94*:12303 (1997). Three N-helices form an interior, trimeric coiled-coil, and three C-helices wrap around the outside of this N-helix coiled-coil along conserved, hydrophobic grooves. This structure likely corresponds to the core of the fusion-active state of gp41 (discussed in D. C. Chan, D. Fass, J. M. Berger, P. S. Kim, *Cell, 89*:263 (1997), and D.C. Chan and Peter S. Kim, *Cell, 93*:681 (1998)) and shows similarity to the proposed fusogenic structures of envelope fusion proteins from influenza (P. A. Bullough, F. M. Hughson, J. J. Skehel, D. C. Wiley, *Nature, 371*:37 (1994)), Moloney Murine Leukemia Virus (D. Fass, S. C. Harrison, P. S. Kim, *Nat. Struct. Biol., 3*:465 (1996)), and simian immunodeficiency virus (SIV). (V.N. Malashkevich, D.C. Chan, C.T. Chutkowski, P.S. Kim, *Proc. Natl. Acad. Sci. USA, 95*:9134 (1998), M. Caffrey *et al.*, *EMBO J., 17*:4572 (1998)), and Ebola virus (W. Weissenhorn *et al.*, *Mol. Cell 2*:605 (1998), V. N. Malashkevich *et al.*, *Proc. Natl. Acad. Sci. USA, 96*:2662 (1999).)

Synthetic C-peptides (peptides corresponding to the C-helix), such as DP178 and C34, are potent inhibitors of HIV-1 membrane fusion and are effective against both laboratory-adapted strains and primary isolates (V. N. Malashkevich, D. C. Chan, C. T. Chutkowski, P. S. Kim, *Proc. Natl. Acad. Sci. USA, 95*:9134 (1998), DP178 corresponds to residues 638-673 of HIV-1 gp41 and is acetylated at the amino terminus and amidated at the carboxy terminus (C. T. Wild, D. C. Shugars, T. K. Greenwell, C. B. McDanal, T. J. Matthews, *Proc. Natl. Acad. Sci. USA, 91*:9770 (1994), S. Jiang, K. Lin, N. Strick, A.R. Neurath, *Nature, 365*:113 (1993)). A Phase I clinical trial with the C-peptide DP178 (also called T-20) indicates that it has antiviral activity *in vivo*, resulting in reduced viral loads (M. Saag, *et al.*, abstract #771 presented at the Infectious Disease Society of America 35th Annual Meeting, San Francisco, CA, 16 September 1997; Kilby, J.M. *et al. Nature Med. 4*:1302-1307 (1998)). Based on the structural features of the gp41 core, these peptides are thought to act through a dominant-negative mechanism, in which exogenous C-peptides bind to the central coiled-coil of gp41 and lead to its inactivation (D.C. Chan and P.S. Kim, *Cell, 93*:681 (1998); R.A. Furuta *et al.*, *Nat. Struct. Biol., 5*:276 (1998); D. C. Chan, D. Fass, J. M. Berger, P. S. Kim, *Cell, 89*:263 (1997), W. Weissenhorn, A. Dessen, S.C. Harrison, J. J. Skehel, D. C. Wiley, *Nature, 387*:426 (1997); K. Tan, J. Liu, J. Wang, S. Shen, M. Lu, *Proc. Natl. Acad. Sci. USA, 94*:12303 (1997), M. Lu, S. C. Blacklow, P. S. Kim, *Nat. Struct. Biol., 2*:1075(1995) and C. H. Chen, T. J. Matthews, C. B. McDanal, D. P. Bolognesi, M. L. Greenberg, *J. Virol., 69*:3771 (1995)). These peptides likely act on a pre-hairpin intermediate of gp41 that forms when the native gp41 structure (i.e., the nonfusogenic conformation present on free virions) is perturbed by gp120/CD4/coreceptor interactions. This pre-hairpin intermediate is proposed to have an exposed N-coiled-coil, thereby allowing C-peptides to bind and inactivate gp41 prior to the formation of the fusion-active hairpin structure (D. C. Chan, P. S. Kim, *Cell, 93*:681 (1998)). This model is further supported by immunoprecipitation experiments indicating that the C-peptide DP178 binds to gp41 (R. A. Furuta, C. T. Wild, Y. Weng, C. D. Weiss, *Nat. Struct. Biol., 5*:276 (1998)). In addition, viruses escaping DP178 inhibition show mutations in the central coiled-coil region of gp41 (L. T. Rimsky, D. C. Shugars, T. J. Matthews, *J.*

Virol., 72:986 (1998)).

Recent crystallographic studies of gp41 facilitate the development of small-molecule peptidomimetic drugs which, in contrast to C-peptides, have the potential to be orally administered. Within each coiled-coil interface is a deep cavity, formed by a cluster of residues in the N-helix coiled-coil, that is an attractive target for the development of antiviral compounds. Three residues from the C-helix (Trp^{628}, Trp^{631}, and Ile^{635}) insert into this cavity and make extensive hydrophobic contacts. Mutational analysis indicates that two of the N-helix residues (Leu^{568} and Trp^{571}) comprising this cavity are critical for membrane fusion activity (J. Cao, *et al., J. virol., 67*:2747 (1993)). Therefore, it is reasonable to expect that compounds that bind with high affinity to this cavity and prevent normal N– and C-helix pairing will be effective HIV-1 inhibitors. In addition, residues in the cavity are highly conserved among diverse HIV-1 isolates. Because of the high structural conservation, drugs targeting this site would have broad activity against diverse HIV-1 isolates, and possibly HIV-2 isolates.

Although this hypothesis is tempting, until now, it had not been demonstrated that these cavity contacts are important for the potency of the C34 inhibitor. In fact, some C-peptides that lack the cavity-binding residues, such as DP178 (C. T. Wild, D. C. Shugars, T. K. Greenwell, C. B. McDanal, T. J. Matthews, *ibid, 91*:9770 (1994); Kilby, J.M. *et al., Nature Med., 4*:1302 (1998)), are highly effective inhibitors of HIV-1 membrane fusion. These concerns emphasize the need for systematic structure-function analysis to identify determinants of C-peptide activity.

To determine the role of cavity-contacts in inhibitory activity, structure-based mutagenesis was performed on C34. The core of the gp41 ectodomain (Figure 1) was reconstituted with two synthetic peptides called N36 and C34 (M. Lu, P. S. Kim, *J. Biomol. Struct. Dyn., 15*:465 (1997), D. C. Chan, D. Fass, J. M. Berger, P. S. Kim, *Cell, 89*:263 (1997)). Variants of the C34 peptide with single alanine substitutions were synthesized, and the helical content and thermal stability of mutant N36/C34 complexes were quantitated by circular dichroism. As expected, mutation of C34 residues (Met^{629}, Arg^{633}) that do not contact the N36 coiled-coil had

little effect on mean residue ellipticity at 222 nm (a measure of helical content) or stability of N36/C34 complexes (Table 1). However, mutation of the three residues (Trp^{628}→ Ala, Trp^{631}→ Ala or Ile^{635}→ Ala) that project into the N36 coiled-coil cavity resulted in N36/C34 complexes with substantially decreased mean ellipticity and stability (Table 1). The greatest destabilization was observed with the mutant Trp^{631} →Ala, which formed N36/C34 complexes with an apparent melting temperature (T_m) of 37°C, compared to 66°C for wildtype. These results demonstrate that C34 residues making hydrophobic contacts with the N36 coiled-coil cavity are important for stabilizing the helical-hairpin structure of the gp41 ectodomain core.

To determine the importance of these residues in the ability of C34 to inhibit membrane fusion, the activity of C34 peptides was tested in HIV-1 viral entry and syncytium assays (Table 1). Mutations (Met^{629}→ Ala and Arg^{633}→Ala) that had little effect on the stability of the N36/C34 complex also had little effect on the inhibitory activity of wildtype C34 (IC_{50}~2.1 nM and ~0.55 nM for viral entry and syncytium formation, respectively). However, mutation of the strictly conserved Trp^{628} or Trp^{631} to alanine resulted in a substantial decrease in activity of~5 fold and ~30-fold, respectively (Table 1). Mutation of the less well-conserved Ile^{635} resulted in only a ~2-fold decrease in inhibitory activity. These results demonstrate for the first time, the C34 residues which make contact with gp41 pocket are important for the inhibitory potency of C34.

The relationship between the potency of mutant C34 peptides and the stability of mutant N36/C34 complexes was clarified by taking advantage of the greatly destabilizing effect of the Trp^{631} mutation to construct a series of N36/C34 complexes with a gradation of stabilities. The Trp^{631} position was used as a "guest site" and the tryptophan was substituted with natural and artificial amino acids representing a broad range of hydrophobic bulk. In order of increasing hydrophobic bulk, the substitutions were: glycine (Gly), alanine (Ala), L-α-aminobutyric acid (Abu), valine (Val), leucine (Leu), phenylalanine (Phe), the wildtype residue tryptophan (Trp), and L-β-(1-naphthyl) alanine (Nal). This approach resulted in a set of C34 peptides that form N36/C34 complexes with T_ms ranging from 37°C to 66°C. The T_ms and $[\theta]_{222}$(10^3deg cm^2dmol^{-1}) for the N36/C34 variants (with IC_{50}

values (nanomolar) for virus entry and cell fusion, respectively, in parentheses) are: Trp^{631}→Gly, 35°C, 17.1 (38 ± 6.1, 25 ± 3.8); Trp^{631}→Ala, 37°C, -24.9 (40 ± 4.3, 15 ± 0.8); Trp^{631}→Abu, 43°C; -23.2 (16 ± 4.8, 6.9 ± 0.4); Trp^{631}→Val, 43°C, -23.9 (13 ± 2.8, 4.5 ± 0.09); Trp^{631}→Leu, 50°C, -26.7 (5.3 ± 1.0, 3.2 ± 0.1); Trp^{631}→Phe, 59°C, -26.3 (3.6 ± 0.8, 1.6 ± 0.05); wildtype, 66°C, -31.7 (1.5 ± 0.2, 0.55 ± 0.03); Trp^{631}→Nal, 62°C, -32.0 (1.4 ± 0.3, 0.79 ± 0.08). The concentration of the Trp^{631}→Nal peptide was measured by Nal absorbance using the extinction coefficient ε = 6900 at 282 nm (J. Blake, C. H. Li, *J. Med. Chem., 18*:423-426 (1975)). In HIV-1 infection and syncytium assays, this series of peptides showed potencies that closely correlated with the T_m of the corresponding N36/C34 complex (Figure 2). The potency order of these mutants is wt~Nal>Phe>Leu>Val~Abu>Ala~Gly, in close agreement with the hydrophobic bulk of the substitution and the stability of N36/C34 complexes. There is a striking linear relationship when the IC_{50} is plotted on a logarithimic scale as a function of the $_{Tm}$ (Figure 2). Since $\Delta G = -RTInK$ (ΔG, change in free energy; R, gas constant; T, absolute temperature; and K, equilibrium constant) and ΔT_m ($T_{m.\ wildtype\ complex} - T_{m.\ mutant\ complex}$) is proportional to $\Delta(\Delta G)$ ($\Delta G_{\ wildtype\ complex} - \Delta G_{\ mutant\ complex}$) (W. J. Becktel, J.A. Schellman, *Biopolymers, 26*:1859 (1987)), the observed linear relationship strongly suggests that the potency of the C34 variants is directly related to their affinity for the N-helix coiled-coil, as predicted by a dominant-negative mode of inhibition. These results provide strong support for the proposal that the coiled-coil cavity in the gp41 core is an attractive drug target. Conserved residues projecting into the hydrophobic cavity clearly play a major role in the ability of C34 to inhibit HIV-1 infection, indicating that this inhibitor works by forming a high-affinity complex with the N-helix coiled-coil.

Moving beyond traditional peptides, mirror-image phage display techniques (T. N. Schumacher, *et al., Science, 271*:1854 (1996)), selection-reflection aptamer techniques (K.P. Williams *et al., PNAS, 94*:11285 (1997); S. Kluβmann *et al., Nat. Biotech., 4*:1112 (1996); A. Nolte *et al., Nat. Biotech., 14*:1116 (1996), combinatorial chemistry (A. Borchardt, S. D. Liberles, S. R. Biggar, G.R. Crabtree, S.L. Schreiber, *Chem. Biol., 4*:961 (1997); J.C. Chabala, *Curr. Opin. Biotechnol., 6*:632 (1995)) and computational approaches in structure-based drug design (H.

Kubinyi, *Curr. Opin. Drug Discov. Develop., 1*:16 (1998)), can be used to identify D-peptides, peptidomimetics, and small molecules that bind with high affinity to the coiled-coil cavity. The close correlation between N36/C34 stability and C34 inhibitory potency suggests that the effectiveness of such compounds will depend critically on the strength of their cavity-contacts. These results suggest that candidate compounds can be tested for the ability to form a stable complex with N36, thereby providing a basis for rapid, quantitative screens to identify and evaluate potential inhibitors of HIV-1 entry.

Small-molecule inhibitors directed against the cavity of the central coiled-coil target one of the most highly conserved regions of the HIV-1 envelope proteins. The analogous cavity in the SIV gp41 core has an essentially identical structure, with conservation of side chain conformations (V. N. Malashkevich, D. C. Chan, C. T. Chutkowski, P. S. Kim, *Proc. Natl. Acad. Sci. USA, 95*:9134 (1998)). This high degree of structural conservation explains the broad neutralizing activity of C-peptides, which are effective against laboratory-adapted strains as well as primary isolates (C. T. Wild, D. C. Shugars, T. K. Greenwell, C. B. McDanal, T. J. Matthews, *Proc. Natl. Acad. Sci. USA, 91*:9770 (1994), S. Jiang, K. Lin, N. Strick, A.R. Neurath, *Nature, 365*:113 (1993)). Remarkably, SIV C34 peptide is nearly as effective as HIV-1 C34 in inhibiting HIV-1 infection (V. N. Malashkevich, D. C. Chan, C. T. Chutkowski, P. S. Kim, *Proc. Natl. Acad. Sci. USA, 95*:9134 (1998)). In addition, a C-peptide (T649) containing the cavity-binding region is much less susceptible to the evolution of resistant virus (L. T. Rimsky, D. C. Shugars, T. J. Matthews, *J. Virol., 72*:986 (1998)) than DP178 (also called T-20), which lacks this region. These observations are evidence that high-affinity ligands targeting the coiled-coil surface, particularly its cavity, will have broad activity against diverse HIV isolates (including HIV-2) and will be less likely to be bypassed by drug-escape mutants.

These studies on the mechanism of C-peptide action also support the hypothesis that the trimeric hairpin structure of the gp41 core (Chan, D.C. *et al.*, *Cell, 89*:263 (1997); Weissenhorn, W. *et al.*, *Nature, 387*:426 (1997); Tan, K. *et al.*, *Proc. Natl. Acad. Sci. USA. 94*:12303 (1997)) corresponds to the fusion-active state

of gp41. The work described herein shows that the inhibitory potency of C34 depends on its ability to bind to the N-coiled-coil of gp41. Since the hairpin structure of gp41 is extremely stable (with a melting temperature in excess of 90°C) (Lu, M. *et al.*, *Nat. Struct. Biol.*, *2*:1075 (1995)), it is unlikely that nanomolar concentrations of C34 can disrupt this structure once it has formed, especially given the high effective concentration of the N– and C-helices within an intact gp41 molecule. Rather, C-peptides likely act prior to the formation of the gp41 hairpin by binding to a transient pre-hairpin intermediate, in which the central coiled-coil is exposed. Binding of C-peptides to this pre-hairpin intermediate inactivates gp41 and prevents its conversion to the fusion-active hairpin structure (D. C. Chan, P. S. Kim, *Cell*, *93*:681 (1998)).

As described herein, the pocket on the surface of the N-helix coiled-coil of HIV-1 envelope protein gp41 subunit is a drug target. Similarly, cavities on other pathogens (e.g., HIV-2) which can cause AIDS or on pathogens which cause AIDS-like conditions in nonhuman mammals (e.g., SIV) are also drug targets. As described herein, available methods (e.g., mirror image phage display methods, combinational chemistry, computational approaches and other drug screening and medicinal chemistry methods) can be used to identify peptides, D-peptides, peptidomimetics and small molecules that bind the coiled-coil cavity of HIV-1 (and/or HIV-2) with sufficient affinity to interfere with viral entry into cells and, thus, inhibit viral infection. As further described herein (Example 3), mirror image phage display has been used to identify D-peptides which bind to a cavity on the surface of the N-helix coiled-coil of HIV-1 gp41.

As a result of the work described herein, screening assays which identify molecules or compounds (agents or drugs) that prevent C34/N36 complex formation and/or disrupt the complex once it has formed are available, as are methods of identifying molecules or compounds (agents or drugs) which bind the N-helix coiled-coil pocket of HIV gp41. Such drugs or agents are useful to inhibit (totally or partially) HIV entry into cells and, thus, infection by HIV.

Methods of screening for compounds or molecules (referred to as drugs or agents) that interfere with formation of a stable complex between C34 and N36 or

disrupt a complex between the two and methods of screening for compounds or molecules that bind the N-helix coiled-coil pocket of HIV gp41 are a subject of the present invention.

In one embodiment of a screening method of the present invention, drugs which interfere with formation of a complex between C34 peptide and N36 peptide are identified by combining a candidate drug (a compound or molecule to be assessed for its ability to interfere with formation of a complex between C34 and N36) with C34 and N36, thus forming a test sample, under conditions appropriate for formation of a complex between C34 and N36 and determining whether formation of C34/N36 complex is inhibited (partially or totally) in the test sample. Results of this assessment can be compared with the results of an appropriate control, which is the same combination as the test sample, except that the candidate drug is not present; the control is subjected to the same conditions as is the test sample. If C34/N36 complex is not formed or is formed to a lesser extent in the presence of the candidate drug (in the test sample) than in its absence, the candidate drug is a drug that interferes with formation of a stable complex between C34 and N36. Such a drug is also referred to herein as an inhibitor of C34/N36 complex formation. Inhibition of complex formation can be assessed by determining the extent to which binding of the two members of the complex occurs, such as by means of a fluorescence assay (e.g., FRET), in which C34 and N36 are each labeled by a member of a pair of donor-acceptor molecules or one end of one of the peptides (e.g., the N-terminus of C34) is labeled with one member of such a pair (EDANS) and the natural fluorophore tryptophan, present in the N36 peptide, is the other member of the donor/acceptor pair. Binding of the C34 and N36 is assessed by the extent to which light emission (FRET) occurs from the acceptor model and/or the wavelength spectrum of the light emitted is altered. Prevention of binding by the candidate drug alters the extent to which light is emitted and/or prevents the shift in wavelength that would occur if binding of C34 and N36 occurred. Alternatively, C34 can be labeled with a detectable label, such as a radiolabel (e.g., by synthesizing a variant C34 with a kinase recognition site that can be labeled with a kinase and radioactive ATP). The radiolabeled C34 and the candidate drug are combined with

N36 immobilized to, for example, a solid surface (e.g., a bead or a plastic well), thus producing a test sample. The extent to which binding of labeled C34 with immobilized N36 occurs is determined and compared with the extent to which binding of labeled C34 to immobilized N36 occurs under the same conditions to which the test sample is subjected, but in the absence of the candidate drug (in a control sample). Typically, this assessment is carried out after the sample has been maintained for sufficient time and under appropriate conditions for C34/N36 binding to occur and a subsequent wash to remove any unbound C34 and candidate drug. If binding occurs in the test sample to a lesser extent than in the control sample, as evidenced by less radiolabel bound to the immobilized N36 in the test sample than in the control sample, the candidate drug is an inhibitor of binding of C34 and N36. Alternatively, the label or tag on C34 can be a member of a binding pair, the other member of which is used to detect binding to N36. For example, C34 can be tagged with biotin (through standard solid-state peptide synthesis, for example) and combined with N36, which can be in solution or bound to a solid surface, such as a bead, well or flat/planar surface, along with the candidate drug (test sample) or in the absence or the candidate drug (control sample). Binding of C34 to N36 is assessed by detecting the presence of biotin associated with N36, such as through the use of labeled streptavidin (e.g., streptavidin - HRP, streptavidin - AP or iodinated streptavidin), which binds the biotin on C34 and is then itself detected through its label. If binding occurs less in the presence of the candidate drug (in the test sample) than in the absence of the candidate drug (in the control sample), as indicated by the presence of less biotin detected on N36 in the test sample than in the control sample, the candidate drug is an inhibitor of C34/N36 binding. The candidate drugs can be obtained, for example, from a library of synthetic organic compounds or random peptide sequences, which can be generated synthetically or through recombinant technology.

In a similar fashion, the ability of a candidate drug to disrupt C34/N36 binding can be assessed, to identify inhibitors of C34/N36 and, thus, of HIV infection. In this embodiment, preformed C34/N36 complex is combined with a candidate drug, which is to be assessed for its ability to disrupt the complex, thus

producing a test sample. The control sample is the same as the test sample, except that the control sample does not contain the candidate drug; it is treated in the same manner as the test sample. If C34/N36 binding is disrupted in the presence of the candidate drug and not in the control sample or if disruption of the complex occurs to a greater extent in the test sample than in the control sample, the candidate drug is an inhibitor (disrupter) of C34/N36. Detection of disruption of binding can be carried out as described above for detection of/prevention of/interference with binding of C34/N36 (e.g., by FRET or a fluorescence assay, by detecting a radiolabel or other detectable label, such as biotin.)

Results described herein demonstrate that hybrids (i.e., fusion proteins) can be made between a trimeric version of the coiled-coil region of a protein (such as GCN4) and the N-helix coiled-coil of HIV gp41, and that such hybrids are trimeric (i.e., not aggregated) and 100% helical. Results described herein also clearly indicate that such fusion proteins do not disrupt or alter the structure of the N-peptide large cavity (i.e., hydrophobic pocket), which is essentially the same in IQN17 (ligand-free and in complex with D10pep1; see Example 5) as it is in N36 (i.e., in complex with C34; Chan D.C. *et al. Cell,* 89, 263 (1997)).

Figures 5A, 5B and 6 present results of assessment of peptides described herein. In Figure 5A-5B, the IQN17 crystal structure is shown to be a continuous, three-stranded coiled-coil; the 17 residues derived from HIV gp41 form a hydrophobic pocket very similar to that found in the crystal structure of gp41. As shown, D10pep1 is bound to this pocket and the residues of D10pep1 that correspond to the conserved residues (leucine, tryptophan, tryptophan) found in all of the D-peptide inhibitors described herein are packed into this pocket, clearly indicating that other D-peptide inhibitors which comprise these conserved residues would bind to IQN17 in the same manner. Figure 6 shows results of syncytia assays carried out according to the method described by Chan *et al.* (Chan, D. C. *et al. Proc. Natl. Acad. Sci., 95*: 15613-15617 (1998)). In the experiments whose results are represented in Figure 6, D-peptides identified as described herein were used. In each instance, a blocking group (e.g., an acetyl group) was present at the N terminus and a $CONH_2$ (amide) was present at the C-terminus. Results of these assays

showed a range of IC_{50} concentrations, where IC_{50} is the concentration at which one half of the number of syncytia are observed, compared to the control, in which no peptide is included. For example, D10pep5 with two lysines at the N-terminus has an IC_{50} of approximately 6μM.

In another embodiment, the invention relates to a method of identifying a drug that binds the N-helix coiled-coil cavity of HIV gp41. Here, too, the assay is based on assessing loss or decrease in binding, but unlike the C34/N36 complex assay described above, which is a more general assay in that it covers or detects interaction with any portion of the groove formed by the N-helical region of HIV gp41, this embodiment focuses on the HIV gp41 hydrophobic pocket (the N-helix coiled-coil cavity). In this embodiment, the method comprises combining a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 with a fusion protein that comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity, under conditions appropriate for presentation of the HIV gp41 cavity for binding by a peptide or other molecule and determining (e.g., in a high throughput screen) whether the candidate drug binds the fusion protein. If binding occurs, the candidate drug is a "hit" that may be a drug that binds the N-helix coiled-coil cavity of HIV gp41. If binding occurs, the candidate drug has bound the N-helix coiled coil and it can be determined if it binds to the coiled-coil cavity. Such "hits" can then be screened in secondary assays, such as the cell/cell fusion assay and HIV infectivity assay to determine if the candidate drug is a drug. Alternatively, or in addition, such "hits" can be assessed further by use of a counterscreen with other fusion proteins (or peptides), to which pocket-binding molecules will not bind. For example, GCN4-pI_QI (with the same three surface mutations as in IQN17) or a version of IQN17 with a point mutation in the hydrophobic pocket, IQN17(G39W), in which glycine 39 is mutated to tryptophan, resulting in a large protrusion into the pocket, can be used in a counterscreen. In this example, a candidate drug that binds to IQN17 but not to GCN4-pI_QI (with the same three surface mutations as in IQN17) or IQN17(G39W) is a drug that binds the N-helix coiled-coil cavity of HIV gp41.

In a further embodiment, a competitive assay is carried out. In this

embodiment, a peptide or protein that binds the N-helix coiled-coil cavity of HIV gp41 is combined with the candidate drug and the fusion protein and whether the candidate drug binds the HIV gp41 cavity is determined in the presence of the peptide that binds the N-helix coiled cavity of HIV gp41. If the candidate drug binds the fusion protein, it is a drug that binds the HIV gp41 cavity. For example, a fusion protein which comprises a trimeric version of the coiled-coil region of GCN4 and the C-terminus of the N peptide of HIV gp41 that includes the N-helix coiled-coil cavity (IQN17) is combined with a "reference" D-peptide (e.g., any of the D-peptides described herein or variants thereof) that binds the N-helix coiled-coil cavity and a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41, thus producing a test sample, which is maintained under conditions appropriate for binding of the D-peptide to bind to the cavity. A control sample, which includes the same components as the test sample, except for the candidate drug, and is handled in the same manner as the test sample, is also assessed. In both samples, binding of the reference D-peptide is assessed. If binding of the reference D-peptide occurs to a lesser extent in the presence of the candidate drug (in the test sample) than in its absence (in the control sample), the candidate drug is a drug that binds the N-helix coiled-coil cavity of HIV gp41. Detection of binding is assessed, for example, in a similar manner as described above for the C34/N36 embodiment of the invention. For example, the D-peptide is labeled with a detectable label, such as a radiolabel or a first member of a binding pair (e.g., biotin), and the extent to which the N-helix coiled-coil cavity bears the label (after the samples have been maintained under conditions appropriate for binding of the reference D-peptide to the cavity) is determined. In the case in which radiolabeling is used, the extent to which the fusion protein bears the radiolabel is assessed in the test sample and compared with the extent to which the fusion protein bears the radiolabel in the control sample. If the detectable label is a first member of a binding pair (e.g. biotin), the second member of the pair (a binding partner) is added to the samples in order to detect the extent to which the fusion protein is bound by the reference D-peptide. This can be done directly or indirectly (e.g., by adding a molecule, such as an antibody or other moiety which binds the second

member of the binding pair). Less of the label will be present on the fusion protein (N-helix coiled-coil cavity) if the candidate drug has inhibited (totally or partially) binding of the D-peptide to the cavity. If binding occurs to a lesser extent in the test sample (in the presence of the candidate drug) than in the control sample (in the absence of the candidate drug), then the candidate drug is a drug that binds the N-helix coiled-coil cavity of HIV gp41.

IQN17, or a variant thereof, in the D-enantiomer, is useful to identify molecules or compounds which are members of a library or collection and bind the N-helix coiled-coil of gp41. For example, a library or collection of molecules or compounds, such as a phage display library, can be screened with IQN17 in the D-enantiomer to identify members that bind the pocket. This has been carried out successfully, as described herein. The mirror image of IQN17, or a variant thereof, is used as the target molecule. As used herein, the terms "D-enantiomer of a polypeptide" and "D-peptide" refer to the exact mirror image of the molecule in the natural handedness. Thus, for amino acid residues that contain a second chiral center, such as Ile and Thr, the exact mirror image of the naturally-occurring amino acid residue is used to create the D version of the polypeptide. Also as used herein, the terms "D-amino acids" and "L-amino acids" are both meant to include the non-chiral amino acid glycine. D-IQN17 can be immobilized to a solid surface, such as by addition of one member of a binding pair (e.g., biotin) to it and addition of the other member of the pair (e.g., streptavidin) to the solid surface. Binding of the two members results in immobilization of D-IQN17 on the solid surface, such as for phage panning. A linker which is an enzyme recognition site (e.g., an amino acid linker such as Gly-Lys-Gly, in which an L-lysine residue is used) can be placed between the D-IQN17 sequence and the binding pair member (between the biotin and D-IQN17) to provide an enzyme recognition site (here, a trypsin recognition site), so that bound phage can be eluted by a trypsin digestion, rather than by non-specific elution, such as acid addition. The phage display library can be a library of L-amino acid peptides of any appropriate length fused to an appropriate phage gene. In one embodiment, it is a phage display library of L-amino acid peptides fused to the gIII gene of M13 phage. The peptides, in one embodiment, comprise 10

randomly encoded amino acid residues flanked by either a cysteine or a serine on both sides. Typically, several rounds of panning are carried out. D-IQN17-specific binding phage are identified. Phage that bind only the gp41 region of D-IQN17 can be identified by post-panning assessment, such as by screening against wells that lack the antigen and then further testing against a panel of molecules. For example, specific pocket-binding phage include those that bind D-IQN17 but not D-GCN4-pI_QI (with the same three surface mutations as in IQN17) or a version of D-IQN17 with a point mutation in the hydrophobic pocket, D-IQN17(G39W), in which glycine 39 is mutated to tryptophan, resulting in a large protrusion into the pocket. D-peptides identified in this manner can be assessed for their ability to inhibit HIV gp41, using known assays, such as the cell/cell fusion assay and HIV infectivity assay. The mirror-image phage display method described herein has demonstrated the value of IQN17 and IQN17(G39W), and their D-enantiomers in identifying inhibitors of HIV-1 entry that bind the gp41 pocket. Of nine specific pocket-binding phage sequences identified (phage that bind to D-IQN17 but not to D-IQN17(G39W), eight contain a consensus EWXWL sequence and inhibit HIV-1 gp41-induced syncytia formation when tested as D-peptides. The ninth peptide was toxic to cells and was not investigated further.

The D-versions of IQN17 and IQN17(G39W) can be used in a similar manner with other biologically encoded libraries, to discover other pocket-binding molecules that are not subject to enzymatic degradation by natural enzymes. For example, other phage-display libraries can be used to identify new D-peptide inhibitors (e.g., with a different number of residues between the flanking Cys residues and/or with randomly encoded amino acid residues outside the regions flanked by cysteine residues and/or with more than two cysteine residues). Strategies for encoding peptide libraries without phage (e.g., in which the encoding mRNA is attached to the peptide) can be used to identify D-peptide inhibitors. RNA or DNA libraries can be used (e.g., with SELEX methods) to identify L-ribose- or L-deoxyribose-based RNA or DNA aptamers, respectively, that bind to the hydrophobic pocket and are not substrates for natural nucleases (see e.g., Williams *et al.*, *PNAS, 74*:11285 (1997)).

Although the versions of IQN17 and IQN17(G39W) of natural L-handedness can also be used in similar manner with biologically encoded libraries, the most likely applications will be with other, non-biologically encoded libraries. For example, chemical combinatorial libraries on beads (of the one-bead, one-compound variety) can be screened with labeled IQN17 (e.g., radioactive or with a chromophore) to identify beads containing molecules that bind to IQN17. In this example, IQN17(G39W) can be used as a counterscreen to determine if the molecules on the bead bind to the pocket of IQN17. (If they bind to IQN17(G39W), then they are not likely to be pocket-binding molecules.) As another example, beads to which IQN17 had been previously attached can be incubated with a mixture of potential pocket-binding molecules (e.g., a mixture of chemicals, or a natural product extract). IQN17 (bound to the beads) can then be separated from the mixture, washed, and then subjected to conditions (e.g., organic solvent, low pH, high temperature) that elute molecules bound to the IQN17 on the beads. The eluted molecules (i.e., potential pocket-binding molecules) could be identified by analytical chemistry methods (e.g., HPLC, mass spectrometry). A counterscreen with IQN17(G39W) is useful to help to identify true pocket-binding molecules.

Drugs identified by the methods described above are then further tested for their ability to inhibit (totally or partially) HIV gp41 function (membrane fusion) and, thus entry into cells, using further *in vitro* assays, such as the syncytium assays and/or infectivity assays described herein or others known to those of skill in the art, and/or *in vivo* assays in appropriate animal models or in humans.

One embodiment of the present invention is a method of identifying a drug that binds the N-helix coiled-coil of HIV gp41, particularly the N-helix coiled-coil pocket. The method comprises combining a candidate drug to be assessed for its ability to bind the N-helix coiled-coil pocket of HIV gp41 and peptide which comprises a soluble, trimeric coiled-coil and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 pocket, under conditions appropriate for presentation of the HIV gp41 pocket for binding by a molecule or compound (e.g., a drug) and determining whether the candidate drug binds the HIV gp41 pocket. If binding of the candidate drug with the HIV gp41 pocket occurs, the candidate drug

is a drug which binds the N-helix coiled-coil pocket of HIV gp41. Optionally, binding of the candidate drug can be assessed in the assay as described above, except that a peptide that binds the N-helix coiled-coil pocket (a peptide previously identified as one which binds the pocket) is combined with the candidate drug and the peptide. In this competitive assay, binding of the candidate drug to the N-helix coiled-coil pocket is assessed in the presence of a known binding moiety (a molecule or compound which binds the pocket). If binding of the candidate drug occurs in the presence of the known binding moiety, the candidate drug is a drug which binds the N-helix coiled-coil pocket with sufficient affinity to successfully compete with the known binding moiety. The fusion protein used in this embodiment comprises a soluble, trimeric version of a coiled-coil, such as a soluble, trimeric version of the coiled-coil region of a protein (e.g., a non-HIV protein, such as that of GCN4 or GCN4-pI$_Q$I, although an HIV protein can be used) and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity. For example, this portion can comprise SEQ ID NO.: 20 or a sufficient portion to comprise the cavity and, when present in an appropriate fusion protein or other soluble model, present the cavity in such a manner that it is available for binding. Alternatively, a variant of the HIV gp41 sequence present herein, a sequence from another strain of the human virus (e.g., HIV-2) or a sequence from another species (e.g., SIV, feline immunodeficiency virus, Visna virus (M. Singh *et al.*, *J. Mol. Biol., 290*:1031 (1999)) can be used in the fusion protein or soluble model. The fusion protein can comprise a soluble, trimeric version of the coiled-coil of any protein, provided that when it is in the fusion protein with the HIV component, the HIV cavity is presented in such a manner that it is available for binding. It can be, for example, that of GCN4-pI$_Q$I, GCN4-pII, Moloney Murine Leukemia Virus (Mo-MLV) or the ABC heterotrimer. In one embodiment, the fusion protein is IQN17 in the D- form. In another embodiment, the fusion protein is IQN17 in the natural L-handedness.

In the competitive assay format, any peptide known to bind the N-helix coiled-coil cavity can be used as the known binding moiety. For example, any of the peptides described herein (SEQ ID NOS.: 3-12, 15, 17-19, 23, 24) or a variant or portion thereof can be used. Also, any non-peptide pocket-binding molecule can be

used in the competitive assay format. The competitive assay can be performed in solution, on a bead, or on a solid surface.

In one embodiment, the candidate drug is detectably labeled and binding of the candidate drug to the HIV gp41 N-helix coiled-coil is determined by detecting the presence of the detectable label on the HIV gp41 N-helix coiled-coil (as a result of binding of the labeled candidate drug to the N-helix coiled-coil). Detection of the label on the helix coiled-coil pocket of the soluble model is indicative of binding of the candidate drug to the N-helix coiled-coil pocket and demonstrates that the candidate drug is a drug which binds the N-helix coiled-coil pocket. If the labeled candidate drug is detected on the fusion protein, the candidate drug is a drug which binds the N-helix coiled-coil cavity.

In another embodiment of the method of identifying a drug that binds the N-helix coiled-coil pocket of the HIV gp41, a soluble model that presents the pocket in such a manner that it is available for binding by a drug is combined with a candidate drug and whether binding of the candidate drug with the N-helix coiled-coil of the soluble model occurs is determined. If binding occurs, the candidate drug is a drug which binds the pocket. Here, too, a competitive assay format can be used. The components of the competition assay (e.g., IQN17 and a D-peptide) can be labeled, with any of a variety of detectable labels, including fluorophore/quencher combinations. The candidate drug can be labeled, as described above, with any of a variety of detectable labels. The components of the soluble model (fusion protein) used in this embodiment and the competing moiety which is used in a competitive assay format can also be as described above.

The present invention also relates to a method of producing a drug that binds the N-helix coiled-coil pocket of HIV gp41. In one embodiment, the method is carried out as follows: A soluble model that presents the N-helix coiled-coil pocket of HIV gp41 or a fusion protein which comprises a soluble, trimeric coiled-coil (e.g., of a protein, such as a non-HIV protein, such as GCN4-pI$_Q$I, GCN4-pII, Mo-MLV, ABC heterotrimer or an HIV protein) is combined with a candidate drug to be assessed for its ability to bind the N-helix coiled-coil pocket of HIV gp41 and inhibit entry into cells, under conditions appropriate for presentation of the HIV gp41

pocket for binding by a drug. Whether the candidate drug binds the HIV gp41 pocket is determined, wherein if binding of the candidate drug to the N-helix coiled-coil pocket of HIV gp41 occurs, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41. In this embodiment, the fusion protein comprises a soluble, trimeric coiled-coil (e.g., of a protein such as a non-HIV protein, such as a soluble, trimeric coiled coil of GCN4, GCN4-pIQI, GCN4-pII, Mo-MLV, ABC heterotrimer or an HIV protein) and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 N-helix coiled-coil pocket (e.g., all or a portion of SEQ ID NO.: 20, a variant or modification thereof or a sequence from another strain or species). IQN17, described herein, can be used in this method; the D enantiomer of IQN17 can also be used (e.g., in mirror-image phage applications). The ability of the drug produced to inhibit HIV entry into cells is assessed, for example, in a syncytium assay and/or an infectivity assay, as described herein. It can be further assessed in an appropriate animal model or in humans.

The invention also relates to a method of producing a drug that binds the N-helix coiled-coil pocket of HIV gp41. The method comprises: producing or obtaining a soluble model of the N-helix coiled-coil pocket of HIV gp41 (e.g., a fusion protein as described herein and particularly IQN17 or a variant thereof); combining a candidate drug (a molecule or compound) to be assessed for it ability to bind the N-helix coiled-coil pocket of HIV gp41 and the soluble model of the N-helix coiled-coil pocket of HIV gp41 and determining whether the candidate drug binds the N-helix coiled-coil pocket of HIV gp41. If the candidate drug binds the N-helix coiled-coil pocket of HIV gp41, the candidate drug is a drug which binds the N-helix coiled-coil pocket of HIV gp41; as a result, a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced. The fusion protein used in this embodiment is described herein and can be, for example, IQN17, the D enantiomer of IQN17, or variants thereof. Alternatively, a drug that binds the N-helix coiled-coil pocket of HIV gp41 and inhibits entry of HIV into cells can be produced by a method comprising: producing or obtaining a soluble model of the N-helix coiled-coil pocket of HIV gp41, as described herein; combining the soluble model and a candidate drug to be assessed for its ability to bind the N-helix coiled-coil pocket of

HIV gp41; determining whether the candidate drug binds the N-helix coiled-coil pocket of the soluble model (fusion protein), wherein if binding occurs, the candidate drug is a drug which binds the N-helix coiled-coil of HIV gp41; and assessing the ability of the drug which binds the N-helix coiled-coil to inhibit HIV entry into cells, wherein if the drug inhibits HIV entry into cells, it is a drug which binds the N-helix coiled-coil pocket of HIV gp41 and inhibits HIV entry into cells. Its ability to inhibit HIV entry into cells can be assessed *in vitro* (e.g., in a syncytium assay, an infectivity assay) or *in vivo* (e.g. in an appropriate animal model or in humans). The soluble model can be a peptide which comprises a soluble, trimeric coiled-coil, such as that of a protein (e.g., GCN4-pI_QI) and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 pocket.

Drugs identified or produced by the methods described herein, as well as by other methods, which bind the N-helix coiled-coil pocket of HIV gp41 and inhibit HIV entry into cells are also the subject of this invention.

Drugs identified or produced by the methods described herein, as well as by other methods, which bind to more than one N-helix coiled-coil pocket of HIV gp41 and inhibit HIV entry into cells are also the subject of this invention. Such drugs can be obtained, for example, by linking two or more pocket-binding molecules (drugs) via an appropriate linker (e.g., a linker of amino aicd residues or other chemical moieties) to increase the effectiveness of inhibition. The pocket-binding molecules that are linked can be the same or different. Drugs identified or produced by the methods described herein or by other methods which bind to the N-helix coiled-coil pocket of HIV gp41, in addition to binding to HIV gp120, CD4, CCR5, CXCR4, or a non-pocket region of HIV gp41 are also the subject of this invention.

Drugs which inhibit HIV gp41 can also be designed or improved with reference to the X-ray crystal structure of the complex between IQN17 and a D-peptide which binds the N-helix coiled-coil cavity presented by IQN17, such as with reference to the X-ray structure of the complex between IQN17 and D10pep1, presented herein. Alternatively, or in addition, drugs which inhibit HIV gp41 can also be designed or improved with reference to the X-ray crystal structure of free IQN17, presented herein.

Compounds and molecules (drugs) identified as described herein inhibit (partially or totally) entry of HIV into cells, and thus are useful therapeutically in uninfected individuals (humans) and infected individuals (e.g., to prevent or reduce infection in an uninfected individual, to reduce or prevent further infection in an infected individual) and as research reagents both to study the mechanism of gp41-induced membrane fusion and to assess the rate of viral clearance by an individual and as reagents to discover or develop other compounds and molecules (drugs) that inhibit entry of HIV into cells. D-peptides described herein (e.g., D10pep5, D10pep1) have been shown, using the infectivity assay described herein, to inhibit infection of cells. Other D-peptides can be similarly assessed for their ability to inhibit infectivity.

The drugs can be administered by a variety of route(s), such as orally, nasally, intraperitoneally, intramuscularly, vaginally or rectally. In each embodiment, the drug is provided in an appropriate carrier or pharmaceutical composition. For example, a cavity-binding drug can be administered in an appropriate buffer, saline, water, gel, foam, cream or other appropriate carrier. A pharmaceutical composition comprising the drug and, generally, an appropriate carrier and optional components, such as stabilizers, absorption or uptake enhancers, flavorings and/or emulsifying agents, can be formulated and administered in therapeutically effective dose(s) to an individual (uninfected or infected with HIV). In one embodiment, drugs which bind the N-helix coiled-coil of gp41 (e.g., those described herein, DP178 (C. T. Wild, D. C. Shugars, T. K. Greenwell, C. B. McDanal, T. J. Matthews, *ibid, 91*:9770 (1994)), T649 which corresponds to residues 117-152 of HIV-1 gp41 (HXB2 strain) and is acetylated at the amino terminus and amidated at the carboxy terminus) (L. T. Rimsky, D. C. Shugars, T. J. Matthews, *J. Virol., 72*:986 (1998), are administered (or applied) as microbicidal agents and interfere with viral entry into cells. For example, a drug or drugs which bind(s) the HIV cavity can be included in a composition which is applied to or contacted with a mucosal surface, such as the vaginal, rectal or oral mucosa. The composition comprises, in addition to the drug, a carrier or base (e.g., a cream, foam, gel, other substance sufficiently viscous to retain the drug, water, buffer) appropriate

for application to a mucosal surface or to the surface of a contraceptive device (e.g., condom, cervical cap, diaphragm). The drug can be applied to a mucosal surface, such as by application of a foam, gel, cream, water or other carrier containing the drug. Alternatively, it can be applied by means of a vaginal or rectal suppository which is a carrier or base which contains the drug or drugs and is made of a material which releases or delivers the drug (e.g., by degradation, dissolution, other means of release) under the conditions of use (e.g., vaginal or rectal temperature, pH, moisture conditions). Such compositions can also be administered orally (e.g., swallowed in capsule, pill, liquid or other form) and pass into an individual's blood stream. In all embodiments, controlled or time release (gradual release, release at a particular time after administration or insertion) of the drug can be effected by, for example, incorporating the drug into a composition which releases the drug gradually or after a defined period of time. Alternatively, the drug can be incorporated into a composition which releases the drug immediately or soon after its administration or application (e.g., into the vagina, mouth or rectum). Combined release (e.g., release of some of the drug immediately or soon after insertion, and over time or at a particular time after insertion) can also be effective (e.g., by producing a composition which is comprised of two or more materials: one from which release or delivery occurs immediately or soon after insertion and/or one from which release or delivery is gradual and/or one from which release occurs after a specified period). For example, a drug or drugs which bind the HIV cavity can be incorporated into a sustained release composition such as that taught in U.S. Patent 4,707,362. The cream, foam, gel or suppository can be one also used for birth control purposes (e.g., containing a spermicide or other contraceptive agent), although that is not necessary (e.g., it can be used solely to deliver the anti-HIV drug, alone or in combination with another non- contraceptive agent, such as an antibacterial or antifungal drug or a lubricating agent). An anti-HIV drug of the present invention can also be administered to an individual through the use of a contraceptive device (e.g., condom, cervical cap, diaphragm) which is coated with or has incorporated therein in a manner which permits release under conditions of use a drug or drugs which bind the HIV gp41 N-helix coiled coil. Release of the drug(s) can occur

immediately, gradually or at a specified time, as described above. As a result, they make contact with and bind HIV and reduce or prevent viral entry into cells.

In another embodiment, a drug which interferes with HIV entry into cells by a mechanism other than binding to the gp41 N-helix coiled-coil cavity (e.g., a drug which interferes with viral entry by interfering with gp120 binding at the CD4 stage) is administered or applied to a mucosal surface as described above for drugs which bind to the gp41 N-helix coiled coil.

Fusion proteins of the present invention comprise a soluble, trimeric form or version of a coiled-coil, such as a soluble, trimeric form or version of a coiled-coil region of a protein (of non-HIV origin or of HIV origin) and a sufficient portion of the C-terminal end of the N peptide of HIV gp41 to include (comprise) the HIV coiled-coil cavity or hydrophobic pocket (the pocket-comprising residues of the N-peptide). The N peptide of HIV gp41 can be that of HIV-1, HIV-2, another HIV strain or a strain from another species (e.g., simian immunodeficiency virus (SIV), feline immunodeficiency virus or Visna virus). For example, HIV-2 sequence LLRLTVWGTKNLQARVT (SEQ ID NO: 26), SIV sequence LLRLTVWGTKNLQTRVT (SEQ ID NO: 27) or a sequence comprising invariant residues in HIV-1, HIV-2 and SIV (represented LLXLTVWGXKXLQXRXX (SEQ ID NO: 42), wherein amino acid residues L, T, V, W, G, K, Q, and R are the single letter code used for amino acid residues and X can be any amino acid residue). Also the subject of this invention is a soluble trimeric model of the HIV gp41 hydrophobic pocket, which can be a D-peptide or an L-peptide and comprises a soluble trimeric coiled coil and a sufficient portion of the N peptide region of HIV gp41 to comprise the amino aicd residues which form the pocket of the N-helix coiled-coil region of HIV gp41. The D- or L-peptide can comprise as the soluble, trimeric coiled coil the coiled coil of GCN4-pI$_Q$I, of GCN4-pII, of Moloney Murine Leukemia Virus or of the ABC heterotrimer. The component which is a sufficient portion of the N peptide of HIV gp41 to comprise the amino acid residues of the pocket can comprise, for example: LLQLTVWGIKQLQARIL of HIV-1 (SEQ ID NO: 20); LLRLTVWGTKNLQARVT of HIV-2 (SEQ ID NO: 26); LLRLTVWGTKNLQTRVT of SIV (SEQ ID NO: 27) or the invariant residues of

these, which are: LLXLTVWGXKXLQXRXX (SEQ ID NO: 42).

One embodiment of the instant invention are fusion proteins between a trimeric version of the coiled-coil region of a protein (such as GCN4-pI_QI) and the N-helix coiled-coil of HIV gp41 that include all, part or none of the N-helix cavity. That is, a fusion protein of the present invention can comprise a trimeric form of the coiled-coil region of GCN4-pI_QI and a portion of the N-peptide of HIV-1 gp41, wherein the portion of the N-peptide of gp41 comprises part, or all, or none of the N-helix cavity of HIV-1 gp41. For example, a fusion protein can be made that contains residues from GCN4-pI_QI and residues from N36. The fusion protein, denoted IQN24n, contains 29 residues of GCN4-pI_QI, including three mutations for increased solubility, and 24 residues from the N-terminal end of N36 (SGIVQQQNNLLRAIEAQQHLLQLT) (SEQ ID NO 21); for recombinant expression in E. coli, an extra Met residue is included at the N-terminus. For example, a fusion protein can comprise a portion of the N-peptide of HIV gp41 comprising the amino acid sequence of (SEQ ID.: 21). The sequence of IQN24n is: MRMKQIEDKIEEIESKQKKIENEIARIKKLISGIVQQQNNLLRAIEAQQHLLQL T (SEQ ID.: 22). This fusion protein can be made by a variety of methods, including chemical synthesis or recombinant DNA methods or by recombinant expression in E. coli, in which case the N– and C-termini are not blocked. Because the superhelix parameters of the GCN4-pI_QI coiled coil are nearly identical to the HIV gp41 N-helix coiled coil, the resulting fusion protein molecule (IQN24n) is predicted to form a long trimeric coiled coil, which presents part of the gp41 N-helix coiled coil as a trimer (not aggregated).

An alternative embodiment of the instant invention provides a method of eliciting an immune response in an individual. The strategy used to create a soluble, trimeric model for part of the gp41 N-terminal region coiled coil is also helpful to develop HIV vaccine candidates. One goal for a potential HIV vaccine is to elicit a neutralizing antibody response that binds to the "pre-hairpin" intermediate of the HIV-1 gp120/gp41 envelope protein complex. In this transient form, the N-helix region of gp41 is exposed, but the C-helix region is not. Although it seems reasonable to use an N-peptide (such as N36, N51 or DP-107) as an immunogen to

elicit an antibody response against the N-helix region of gp41, the isolated N-peptides are aggregated and do not properly present the gp41 N-helix coiled-coil trimer. Accordingly, the same strategy described herein to solve this problem for the gp41 hydrophobic pocket can be applied towards the development of soluble, trimeric models of the gp41 N-helix coiled-coil region, in general. Such trimeric models (including IQN 17, but also including, for example, peptides that do not contain the pocket residues of gp41) can be used as immunogens to elicit an antibody response to the pre-hairpin intermediate, thereby inhibiting HIV-1 infection. For example, an individual to be immunized can be administered a fusion protein comprising a trimeric form of a coiled-coil region of a protein and a portion of an N-peptide from HIV-1 gp41, wherein the portion from gp41 comprises part of, all of, or none of the N-helix coiled-coil cavity in a pharmaceutically acceptable carrier. For example, IQN24n can be used, either alone or in combination with other materials, in a vaccine, which will elicit the production of antibodies that bind to the coiled coil in the individual to whom it is administered (the vaccinee), and thereby offer protection against infection and/or disease. IQN24n can also be used to identify (from humans, other animals or antibody libraries) and/or raise antibodies (monoclonal and/or polyclonal) that bind to the N-helix coiled coil. This provides the basis for a diagnostic method in which IQN24n (or IQN17 or other soluble trimeric model) is used to assess the presence/absence/level of antibodies that bind the N-helix coiled coil in a biological sample (e.g., blood).

Any of a wide variety of variations can be made in the GCN4-pI_QI component of fusion proteins described herein (e.g., IQN17 or IQN24n) and used in the method, provided that these changes do not alter the trimeric state of the coiled-coil. Changes can also be made in the amino acid composition of the fusion protein component which is the portion from the HIV gp41 N36 peptide, to produce variants (e.g., variants of IQN17 or IQN24n). There is no limit to the number or types of amino acid residue changes possible, provided that the trimeric state of the coiled-coil and the structure of the surface of the fusion protein corresponding to the N-peptide coiled coil of HIV gp41 are maintained. The fusion protein component which is the portion of the HIV gp41 N-peptide can include all, part, or none of the

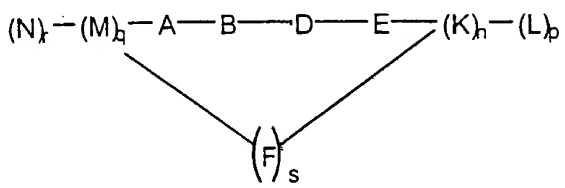
N-helix cavity. For example, other parts of N51, N36, DP-107, or other regions of the HIV gp41 N-helix region can be fused to GCN4-pI$_Q$I (or another trimeric version of the coiled-coil region of a protein) to generate trimeric (not aggregated) helical coiled-coil fusion proteins and used in the method. There is no limit to the number or types of fusion proteins that can be designed and generated, provided that the trimeric state of the coiled-coil and the structure of the surface of the fusion protein corresponding to the N-peptide coiled coil of HIV gp41 are maintained. Such fusion proteins can be designed and generated using methods known to those of skill in the art, such as evaluating heptad-repeat positions or superhelix parameters of coiled coils.

Described herein are peptides, which can be D-peptides or L-peptides, which bind to a cavity on the surface of the N-helix coiled-coil of HIV envelope glycoprotein gp41 (e.g., HIV-1, HIV-2). Such peptides can be of any length, provided that they are of sufficient length to bind the cavity in such a manner that they interfere with the interaction of the N-helix coiled-coil cavity and amino acid residues of the C-peptide region of HIV gp41 and prevent HIV entry into the cells. For example, D- or L-peptides comprise at least two amino acid residues and generally will be from about two to about 21 amino acid residues. That is, they can comprise any number of amino acid residues from about two to about 21. The amino acid residues can be naturally occurring or non-naturally occurring or modified, as described below. The peptides can be linear or circular.

Examples of D-peptides, identified as described herein, are shown in Figure 3. Because of library design, each peptide, in addition to the amino acid residues shown, is flanked by GA on the N-terminus and AA on the C-terminus. N-terminal lysine residues were added to improve water solubility.

In one embodiment, the present invention provides compounds which inhibit the binding of the N-helix coiled coil to the C-helix of HIV-1 gp41 envelope protein. Such compounds are of use in a method of treating a patient infected by, or potentially subject to infection by, HIV. These compounds are also of use in a method of assessing the ability of a second compound to bind to the N-helix coiled coil cavity.

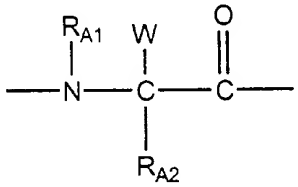
In one embodiment, the compounds which inhibit the binding of the N-helix coiled coil to the C-helix of HIV-1 gp41 envelope protein are of Formula I,



(I),

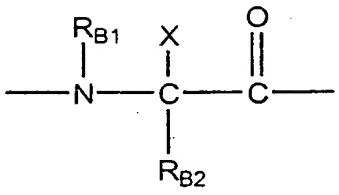
wherein A, B, D and E are each, independently, a D-amino acid residue, an L-amino acid residue, or an N-substituted glycyl residue. Natural or nonnatural amino acid residues can be used. K, L, M and N are each, independently, an amino acid residue or a polypeptide group of from 2 to about 6 amino acid residues which can be the same or different, and n, p, q and r are each, independently, 0 or 1. F is a direct bond or a difunctional linking group and s is 0 or 1.

In one subset of the compounds of Formula I, A is a D- amino acid residue, an L-amino acid residue or an N-substituted glycyl residue of the formula



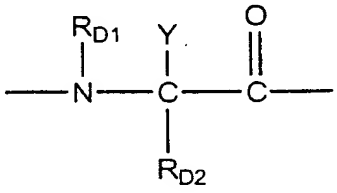
where one of R_{A1} and R_{A2} is a substituted or unsubstituted aryl, heteroaryl, arylmethyl, heteroarylmethyl, benzo-fused aryl, benzo-fused heteroaryl, benzo-fused arylmethyl, benzo-fused heteroarylmethyl, cycloalkyl or bicycloalkyl; and the other is hydrogen. W is hydrogen, methyl, trifluoromethyl or halogen, for example, fluorine, chlorine, bromine or iodine.

B is a glycyl residue or D-amino acid or N-substituted glycyl residue of the formula



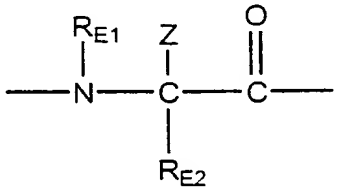
where one of R_{B1} and R_{B2} is a substituted or unsubstituted linear, branched or cyclic alkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group; and the other is hydrogen. X is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine.

D is a D- amino acid residue or N-substituted glycyl residue of the formula



where one of R_{D1} and R_{D2} is a substituted or unsubstituted aryl, heteroaryl, arylmethyl, heteroarylmethyl, benzo-fused aryl, benzo-fused heteroaryl, benzo-fused arylmethyl; benzo-fused heteroarylmethyl, cycloalkyl or bicycloalkyl; and the other is hydrogen. Y is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine.

E is a D-amino acid residue or N-substituted glycyl residue of the formula

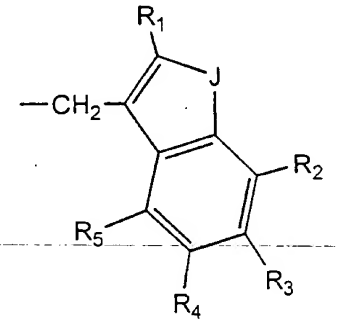


where one of R_{E1} and R_{E2} is a substituted or unsubstituted, linear, branched or cyclic alkyl, aryl or arylalkyl group; and the other is hydrogen. Z is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine.

K, L, M and N are each, independently, composed of from 1 to about 6 (which can be the same or different), D-amino acid residues, L-amino acid residues, N-substituted glycyl residues or a combination thereof. Natural or nonnatural amino

acid residues can be used. One or more of the amino acid residues or N-substiuted glylcyl residues can, optionally, be substituted at the α-carbon by a methyl or trifluoromethyl group, or a halogen, such as a fluorine, chlorine, bromine or iodine atom.

In a preferred embodiment, one of R_{A1} and R_{A2} and one of R_{D1} and R_{D2} are, independently, a phenyl, substituted phenyl, naphthyl, substituted naphthyl, naphthylmethyl, substituted naphthylmethyl, benzyl or substituted benzyl group, or a group of the formula



where J is O, S or NR, where R is H or linear, branched or cyclic C_1-C_6-alkyl, preferably methyl. R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen and alkyl, preferably, linear, branched or cyclic C_1-C_4-alkyl, such as methyl. Suitable phenyl, naphthyl, naphthylmethyl and benzyl substituents include alkyl, preferably linear, branched or cyclic C_1-C_4-alkyl, such as methyl; and halogen, such as flourine, chlorine, bromine or iodine. More preferably, R_{A1} and R_{D1} are both hydrogen, and R_{A2} and R_{D2} are each, ndependently, one of the foregoing groups.

Preferably, one of R_{B1} and R_{B2} is hydrogen, substituted or unsubstituted linear, branched or cyclic C_1-C_4-alkyl, phenyl, benzyl, naphthyl or naphthylmethyl. Suitable substituents include linear, branched or cyclic C_1-C_4-alkyl groups and halogens, such as fluorine, chlorine, bromine or iodine. More preferably, R_{B1} is hydrogen and R_{B2} is one of the foregoing groups.

Preferably, one of R_{E1} and R_{E2} is a substituted or unsubstituted, linear, branched or cyclic C_1-C_6-alkyl group or a substituted or unsubstituted phenyl or

naphthyl group. Suitable substituents include linear, branched or cyclic C_1-C_4-alkyl groups, such as methyl, and halogens, such as fluorine, chlorine, bromine and iodine. More preferably, R_{E1} is hydrogen and R_{E2} is one of the foregoing groups.

In a preferred subset of the compounds of formula I, A and D are each a D-tryptophan residue and E is a D-leucine residue.

Preferably, K is a D-amino acid residue or an N-substituted glycyl residue comprising an amino-, carboxyl- or sulfhydryl substituted side chain, such as a cysteine, glutamic acid, aspartic acid or lysine residue, and L is a polypeptide comprising 2 or 3 D-amino acid residues, L-amino acid residues (the D- or L-amino acid residues can be the same or different) or N-substituted glycine residues. For example, in one embodiment, L comprises 2 or 3 residues selected from among D-glycine, D-alanine or D-α-C_1-C_4-alkylglycine.

Preferably, M is a polypeptide group comprising from 2 to about 8 D-amino acid residues, of which at least one comprises an amino-, carboxy- or sulfhydryl substituted side chain, such as a cysteine, glutamic acid, aspartic acid or lysine residue. N is, preferably, a polypeptide group comprising from 1 to about 6 amino acid residues, of which at least one is a lysine residue.

The identity of divalent linking group F is not critical, as long as it is of a suitable length to position residues A to E to interact with the N-helix coiled coil cavity (J.R. Morphy, *Curr. Op. Drug Discov. Develop.*, *1*:59-65 (1998)). For example, F preferably has a length from about 2 to about 40 atoms. In one embodiment, F is a direct bond or a polypeptide linking group of the formula -P_n-, wherein n is 1 to about 12 and each P is independently an L- or D- amino acid or N-substituted glycyl resdiue residue, a glycyl residue or an N-substituted glycyl derivative.

In another embodiment, F is a substituted or unsubstituted C_4-C_{40}-alkylene group, such as a polymethylene group of the formula -$(CH_2)_m$-, wherein m is from about 4 to about 40; an alkylene group which is interrupted at one or more points by a heteroatom, such as a nitrogen, oxygen or sulfur atom. For example, F can be a group $(CH_2CH_2O)_q$-, wherein q is from 1 to about 20. F can also be an alkylene group which is interrupted at one or more points by a phenylene or heteroarylene

group, or a polysaccharide group, for example, a glycoside or poly(glycoside) group comprising one or more glycoside groups, for example, from 1 to about 10 glycoside groups. Suitable glycosides include glucoside, lactoside, mannoside, galactoside, fucoside, fructoside, guloside, alloside, altroside, taloside, idoside and others, such as pyranosides and furanosides, which are known in the art.

In compounds of Formula I having a C-terminal amino acid residue, the C-terminal residue can be, for example, in the form of an amide, an N-substituted amide or a carboxylic acid protecting group, as is known in the art. The nitrogen atom of an N-terminal residue can be acylated, for example, acetylated, or substituted with an amino protecting group, as is known in the art.

The term "D-amino acid residue", as used herein, refers to an α-amino acid residue having the same absolute configuration as D-glyceraldehyde. When the amino acid residue includes a first non-hydrogen α substituent and a second α substituent selected from methyl and halogen, the absolute configuration is the same as that of D-glyceraldehyde with the second α substituent taking the place of the hydrogen atom at the glyceraldehyde α-carbon.

The peptides, portions of the peptides, variations/derivatives of the peptides or portions of the variations/derivatives described herein can be used as inhibitors of HIV entry into cells. The peptides represented in Figure 3 or a portion of a peptide sufficient to fit into the hydrophobic pocket at the C-terminal end of the coiled-coil and prevent interaction of the C-peptide region with the N-peptide region of gp41 are useful to inhibit HIV infection. A portion of any of the peptides represented or of a derivative thereof can be from 2 to 20 (any number of residues from 2 to 20) amino acid residues in size. D-peptides which comprise the consensus sequence tryptophan-tryptophan-leucine or the sequence tryptophan-tryptophan-leucine-glutamate, described herein, and additional residues, can be used; the other residues present in such D-peptides and the size of the D-peptides can be selected with reference to peptides described herein or can be designed independent of those peptides, provided that these three or four residues are positioned in such a manner that the peptide can fit into the hydrophobic pocket and act as an inhibitor. Additional amino acid residues can also be present at the N-terminus, the C-terminus

or both of the D-peptides described herein, thus producing a larger peptide. Alternatively, there can be other amino acid residues selected, for example, to enhance binding affinity. Alternatively, a peptide which comprises the conserved amino acid residues of the D-peptides of Figure 3 can be used. For example, such a peptide can be 16 amino acid residues in size and include the conserved amino acid residues, which can be at the same positions as those at which they occur in the peptides shown in Figure 3. The intervening amino acid residues can be different from the amino acid residues at these positions in any of the peptides shown in Figure 3 (e.g., can be isoleucine or asparagine or other amino acid residue which does not appear in the peptides represented in Figure 3) or can be substituted for or replaced by an amino acid residue represented at a specific position in another peptide shown in Figure 3 (e.g., the aspartic acid residue in D10pep1 can be replaced by a serine residue). Amino acid residues other than the D-versions of the 20 L-amino acids found in natural proteins can be used. Such changes can be made, for example, to enhance bioavailability, binding affinity or other characteristic of the peptide. A D-peptide can comprise the conserved amino acid residues present in the peptides shown in Figure 3, but they can be separated by fewer (or more) amino acid residues than the number of intervening amino acid residues shown in Figure 3. For example, fewer than five amino acid residues (e.g., Tarrago-Litvak, L. *et al.*, *FASEB, J., 8*:497 (1994); Tucker, T.J. *et al.*, *Methods Enzymol., 275*:440 (1996), Tarrago-Litvak, L. et al., *FASEB, J., 8*:497 (1994); Tucker, T.J. et al., *Methods Enzymol., 275*:440 (1996)), can be present between the first cysteine and the glutamic acid in the consensus sequence shown in Figure 3. Alternatively, these two residues can be separated by more than five amino acid residues. Internal modifications can also be made (e.g., to enhance binding or increase solubility of a peptide). For example, the first tryptophan of D10pep5 can be replaced by an arginine to increase solubility. A D-peptide can have additional moieties or amino acids at its N-terminus. For example, a moiety which blocks the N terminus or gets rid of the charge otherwise present at the N-terminus can be added. The moiety can be, for example, a blocking moiety, such as an acetyl group linked directly to the glycine (G), or an acetyl group linked to one or more additional amino acid residues

linked to the N-terminal of G, such as an acetyl group linked to one or more lysine residues, which, in turn, are linked to the N terminal G. In one embodiment, two lysine residues are linked to the N-terminal G (KKGAC . . . .), for example to increase the solubility of the peptide; a blocking moiety, such as an acetyl group, can be linked to the terminal lysine (acetyl group KKGAC . . . .). In another embodiment, four lysine residues are linked to the N-terminal G. In addition, a D-peptide can have additional and/or altered moieties or amino acids at its C-terminus. For example, one or both of the alanine residues at the C-terminus can be altered and/or one or more residues can be added at the C-terminus, for example to enhance binding. Alternatively, functional (chemical) groups other than amino acid residues can be included to produce an inhibitor of the present invention. For example, these additional chemical groups can be present at the N-terminus, the C-terminus, both termini or internally. In addition, two or more D-peptides can be linked via an appropriate linker (e.g., a linker of amino acid residues or other chemical moieties) to increase the effectiveness of inhibition. Alternatively, one or more D-peptides can be linked via an appropriate linker to a molecule (drug) that binds to HIV gp120, CD4, CCR5, CXCR4, or a non-pocket region of HIV gp41 to increase the effectiveness of inhibition.

The D-peptides (or L-peptides or peptides with both D- and L-amino acids) can be produced using known methods, such as chemical methods or recombinant technology. The polypeptide backbone can be altered (e.g., N-methylation) or replaced with alternative scaffolds (e.g., peptoids) at one or more positions of the peptides. Additional components can be included in the peptides, such as, for example, linkers (chemical, amino acid) which are positioned between amino acids or amino acid portions of the peptide (e.g., to provide greater flexibility or to provide greater rigidity). As described herein, the D-peptides of the present invention are flanked by GA at the N-terminus and AA at the C-terminus, due to the design of the library used in identifying the D-peptides. Some or all of these four amino acid residues may be altered, replaced or deleted in order to produce D-peptides with, for example, altered absorption, distribution, metabolism and/or excretion. In one embodiment, the C-terminus is modified by the addition of a glycine residue

immediately before the C-terminal amide. In another embodiment, the most C-terminal A is altered/modified or replaced by a different amino acid residue or deleted.

D-peptides, which are of the opposite handedness from the handedness of naturally-occurring peptides, do not serve as efficient substrates for enzymes, such as proteases, and, therefore, are not as readily degraded as L-peptides. In addition, there is no effective immune response which targets D-peptides and therefore, they do not elicit an immune response comparable to that elicited by L amino acid peptides.

The present invention is illustrated by the following examples, which are not intended to be limiting in any way.

Example 1 Synthesis of Variants of the C34 Peptide

Mutant peptides were synthesized by solid-phase FMOC peptide chemistry and have an acetylated amino terminus and an amidated carboxy terminus. After cleavage from the resin, peptides were desalted with a Sephadex G-25 column (Pharmacia), and then purified by reverse-phase high-performance liquid chromatography (Waters, Inc.) on a Vydac C18 preparative column using a linear water-acetonitrile gradient and 0.1% trifluoroacetic acid. Peptide identities were verified by MALDI mass spectrometry (Voyager Elite, PerSeptive Biosystems). Peptide concentrations were measured by tryptophan and tyrosine absorbance in 6 M GuHCl [H. Edelhoch, *Biochemistry, 6*:1948 (1967)].

Example 2 Quantitation of Helical Content and Thermal Stability of Mutant N36/C34 Complexes

CD measurements were performed in phosphate-buffered saline (50 mM sodium phosphate, 150 mM NaCl, pH 7.0) with an Aviv Model 62DS spectrometer as previously described (M. Lu, S. C. Blacklow, P. S. Kim, *Nat. Struct. Biol., 2*:1075 (1995)). The apparent melting temperature of each complex was estimated from the

maximum of the first derivative of $[\theta]_{222}$ with respect to temperature. The mean residue ellipticities ($[\theta]_{222}$, 10^3deg cm^2 dmol^{-1}) at 0°C were as follows: wildtype, -31.7; Met^{629}→Ala; -32.0; Arg^{633}→Ala, -30.7; Ile^{635}→Ala, -25.9; Trp^{628}→Ala, -27.0; Trp^{631}→Ala, -24.9. In the case of the Trp^{628}→Ala and Trp^{631}→Ala mutations, the decrease in $[\theta]_{222}$ is likely to overestimate the actual reduction in helical content. The removal of tryptophan residues from model helices has been reported to significantly reduce the absolute value of $[\theta]_{222}$ even when there is little change in helical content (A. Chakrabartty, T. Kortemme, S. Padmanabhan, R. L. Baldwin, *Biochemistry, 32*:5560 (1993)).

Example 3 Identification of Peptides Which Bind to a Pocket on the Surface of the N-helix Coiled-Coil of HIV-1 gp41.

Methods are available to identify D-peptides which bind to a cavity on the surface of the N-helix coiled-coil of HIV envelope glycoprotein gp41. As described in detail below, D-peptides which bind to a cavity on the surface of the N-helix coiled-coil of HIV-1 envelope glycoprotein gp41 were identified by mirror-image phage display. This method involves the identification of ligands composed of D-amino acids by screening a phage display library. D-amino acid containing ligands have a chiral specificity for substrates and inhibitors that is the opposite of that of the naturally occurring L-amino ligands. The phage display library has been used to identify D-amino acid peptide ligands which bind a target or desired L-amino acid peptide (Schumacher *et al. Science, 271:*1854-1857 (1996)).

D-peptides that bind to the hydrophobic pocket of gp41 were identified using a target that is an enantiomer of IQN17, a hybrid molecule containing 29 residues of GCN4-pI$_Q$I on the N-terminal end and 17 residues of gp41 on the C-terminus. The phage library used for selection is described in U.S. Patent 5,780,221 and Schumacher *et al. Science, 271:*1854-1857 (1996). The complexity of the library is greater than 10^8 different sequences. The sequences are flanked on either end by either a cysteine or a serine, with ten random residues in the middle. These sequences are located in the pIII gene of the phage, a coat protein that is expressed as approximately five copies on the outer surface of the phage.

The following experimental procedures were used in the examples described herein.

Phage Display

Neutravidin (Pierce, 10 μg in 100 μL of 100 mM $NaHCO_3$) was added to individual wells of a 96-well high-binding styrene plate (Costar) and incubated overnight on a rocking platform at 4°C. The neutravidin was removed and the wells were washed four times with a TBS/Tween solution. Biotinylated D-IQN17 (100 μL of a 10 μL peptide solution in 100mM $NaHCO_3$) was added to the wells and incubated for one hour at 25°C. The biotinylated target was removed and a blocking solution (30 mg/ml nonfat dried milk in 100 mM $NaHCO_3$) was added to the wells and incubated for two hours, with rocking, at 4°C. The blocking solution was removed and the wells were coated again with the biotinylated target as above. The target was removed and the unliganded neutravidin was blocked by the addition of the blocking solution with 5 mM biotin. After removing the biotin, the wells were washed six times with the TBS/Tween solution. The phage stock was then added to the wells (50 μL of phage stock plus 50 μL of phage-binding buffer: TBS, 0.1% Tween-20, 1 mg/ml milk, 0.05% sodium azide). The incubation time of the phage stock in the wells decreased in increasing rounds of selection. After incubation, the phage solution was removed and the wells were washed twelve times with TBS/Tween to remove the unbound phage. Odd numbered washes were performed quickly, with no incubation time; even numbered washes were incubated for increasing amounts of time each round of phage selection. The phage were eluted by the addition of two micrograms of trypsin in 100 μL of phage-binding buffer and 2.5 mM $CaCl_2$ with an hour incubation at 37°C. To determine recovery, a dilution of the eluted phage was used to infect K 91 kan cells. After a one hour incubation, 100 μL of cells were removed and 1:10, 1:100, and 1:100 dilutions in LB were plated on LB/tetracycline plates. Phage recovery was determined as a ratio of transducing units recovered (the titer of the eluted phage) to the input number of transducing units (the titer of the phage stock used that round). Transducing units were determined by counting the number of tetracycline-resistant colonies on the

LB/tetracycline plates. Non-specific phage recovery generally has a ratio in the order of magnitude of 10^{-8} to 10^{-9}, whereas specifically amplified phage have a ratio 10^{-7} or greater. Individual clones were amplified and sequenced. They were assayed in the binding assay to determine binding specificity.

D10pep7 was identified after five rounds of phage selection. D10pep1, D10pep3, D10pep4, D10pep5, and D10pep6 were identified after seven rounds of phage selection. The phage selection was performed again, with shorter incubation times and longer washes, and D10pep10 and D10pep12 were identified after three rounds of selection. (A ninth D-peptide was identified but was not further investigated once it was shown to be toxic to cells.)

To test the specificity of binding of identified phage clones to the pocket of D-IQN17, the phage clones were added to wells of 96-well plates coated as above with D-INQ17, D-GCN4-pI_QI (with the three mutations), D-IQN17(G39W = glycine36 substituted with tryptophan), or wells with no target. The phage were incubated on the plates and washed for the same lengths of time as in the round from which they were identified. Eluted phage were used to infect K91 kan cells and the recovered transducing units were determined as above. These sequences bound specifically to the wells with D-IQN17.

Peptide Purification

IQN17 and the D10 peptides were synthesized by FMOC peptide chemistry. They have an acetylated N-terminus and a C-terminal amide. IQN17 contains 29 residues derived from GCN4-pI_QI on the N-terminus and 17 residues from the C-terminus of N36 on the C-terminus. There is one residue overlap between GCN4-pI_QI and the N36 region, making the peptide 45 residues long. To improve solubility, three amino-acid substitutions were made in the GCN4-pI_QI region of IQN17, as compared to the original GCN4-pI_QI sequence (Eckert, D.M. *et al.*, *J. Mol. Biol.*, *284*:859-865 1998). These substitutions are L13E, Y17K, and H18K. Thus, the sequence of IQN7 is:

ac-RMKQIEDKIEEIESKQKKIENEIARIKKLLQLTVWGIKQLQARIL-am

(ac- represents an N-terminal acetyl group and -am represents a C-terminal amide),

with the HIV portion underlined. For mirror-image phage display, IQN17 was synthesized using D-amino acids (for amino acid residues that contain a second chiral center, such as Ile and Thr, the exact mirror image of the naturally occurring amino acid residue is used to create the D-version of the target). In addition, the N-terminus of the peptide was biotinylated using NHS-LC-biotin II (Pierce, catalog #21336). Between the biotin and the IQN17 sequence was a three amino acid linker of GKG, with the lysine in the naturally-occurring L-form. This lysine was inserted as a trypsin recognition site.

The sequences of the D-peptides are as follows (with all amino acids in the D-enantiomer, using the exact mirror image of naturally occurring amino acid residues for Ile and Thr, which contain a second chiral center):

D10pep1: Ac-GACEARHREWAWLCAA-$CONH_2$ (SEQ ID NO: 34);

D10pep3: Ac-KKGACGLGQEEWFWLCAA-$CONH_2$ (SEQ ID NO: 15);

D10pep4: Ac-GACDLKAKEWFWLCAA-$CONH_2$ (SEQ ID NO: 35);

D10pep5: Ac-KKGACELLGWEWAWLCAA-$CONH_2$ (SEQ ID NO: 16);

D10pep6: Ac-GACSRSQPEWEWLCAA-$CONH_2$ (SEQ ID NO: 36);

D10pep7: Ac-GACLLRAPEWGWLCAA-$CONH_2$ (SEQ ID NO: 37);

D10pep10: Ac-KKGACMRGEWEWSWLCAA-$CONH_2$ (SEQ ID NO: 18); and

D10pep12: Ac-KKGACPPLNKEWAWLCAA-$CONH_2$ (SEQ ID NO: 19).

After cleavage from the resin, the peptides were desalted on a Sephadex G-25 column (Pharmacia) and lyophilized. The lyophilized peptides were purified by reverse-phase high performance liquid chromatography (Waters, Inc.) on a Vydac C18 preparative column. The D-peptides were then air-oxidized by dissolving the lyophilized powder in 20 mM Tris, pH 8.2, and stirring at room temperature for several days. The oxidized peptides were HPLC purified as before. The expected molecular weights of the peptides were verified using MALDI-TOF mass spectrometry (PerSeptive Biosystems). Peptide concentrations were determined using tyrosine, tryptophan and cysteine absorbance at 280 nm in six molar GuHCl (Edelhoch, 1967). Peptide stock solutions were prepared in DMSO.

The N-terminal lysines on D10pep3, D10pep5, D10pep7a, D10pep10 and

D10pep12 were added to increase the water solubility of the peptides. To investigate the effect of the added lysines on the inhibitory activity of the peptides, D10pep1 was synthesized with two N-terminal lysines (denoted D10pep1a) and compared to D10pep1 without lysines: D10pep1a was found to have an IC_{50} for inhibition of syncytia formation approximately 2-fold higher than D10pep1 (i.e., without lysines). In addition, D10pep5 was synthesized with two additional N-terminal lysines (for a total of four lysines to generate a peptide denoted D10pep5a). The IC_{50} for inhibition of syncytia formation of D10pep5a was approximately 2-fold higher than D10pep5. The addition of N-terminal lysine residues to the D-peptides results in only a modest decrease of inhibitory activity.

D-peptides that had additional D-Lys residues added to the N-termini, that were synthesized for study are indicated with the addition of "a" to the peptide name and include the following:

D10pep1a: Ac-KKGACEARHREWAWLCAA-$CONH_2$ (SEQ ID NO: 38);

D10pep4a: Ac-KKGACDLKAKEWFWLCAA-$CONH_2$ (SEQ ID NO: 39);

D10pep5a: Ac-KKKKGACELLGWEWAWLCAA-$CONH_2$ (SEQ ID NO: 17);

D10pep6a: Ac-KKGACSRSQPEWEWLCAA-$CONH_2$ (SEQ ID NO: 40); and

D10pep7a: Ac-KKGACLLRAPEWGWLCAA-$CONH_2$ (SEQ ID NO: 41).

These sequences are also represented in Figure 3. The 12 amino acid "core" of each D-peptide (which, in turn comprises a 10-mer and the consensus sequences described herein) are as follows:

CDLKAKEWFWLC	(SEQ ID NO: 3)
CEARHREWAWLC	(SEQ ID NO: 4)
CELLGWEWAWLC	(SEQ ID NO: 5)
CLLRAPEWGWLC	(SEQ ID NO: 6)
CSRSQPEWEWLC	(SEQ ID NO: 7)
CGLGQEEWFWLC	(SEQ ID NO: 8)
CMRGEWEWSWLC	(SEQ ID NO: 9)
CPPLNKEWAWLC	(SEQ ID NO: 10)

CVLKAKEWFWLC is an alternative sequence for peptide SEQ ID NO: 3. (SEQ ID NO: 11).

It is readily apparent that there is a highly conserved consensus sequence in these peptides. The 12 amino acid peptide represented in Figure 3 can be represented as: CXXXXXEWXWLC (SEQ ID NO: 12), where amino acid residues common to the peptides are shown and X represents an amino acid residue which is not conserved among the peptides.

Example 4 Assessment of Activity of C34 Peptides and D-Peptides

The potency of C34 peptides in inhibiting viral infection and the HIV-1 infection inhibitory activity of the D-peptides were assayed using recombinant luciferase-expressing HIV-1 (Chen, B.K. *et al.*, *J. Virol.*, *68*:654 (1994); Malashkevich, V.N., *et al. Proc. Natl. Acad. Sci., USA, 95*:9134 (1998)). The virus was produced by co-transfecting an envelope-deficient HIV genome NL43LucR-E- (Chen, B.K. et al., *J. Virol.*, *68*:654 (1994) and the HXB2 gp160 expression vector pCMVHXB2gp160 (see Chan, D.C. *et al.*, *Proc. Natl. Acad. Sci.*, *95*:11513 (1998)) into 293T cells. Low-speed centrifugation was used to clear the viral supernatants of cellular debris. The supernatant was used to infect HOS-CD4/Fusion cells (N. Landau, NIH AIDS Reagent Program) in the presence of the D-peptides, with concentrations ranging from 0 to 500 μM. Cells were harvested 48 hours post-infection, and luciferase activity was monitored in a Wallac AutoLumat LB953 luminometer (Gaithersburg, MD). The IC_{50} is the peptide concentration that results in a 50% decrease in activity relative to control samples lacking peptide. The IC_{50} was calculated from fitting the data to a Langmuir equation [$y=k/(1+([peptide]/IC_{50}) + x]$, where y = luciferase activity and k and x are scaling constants.

Cell/Cell Fusion Assay

Inhibition of cell/cell fusion (i.e., syncytia formation) was assayed by co-culturing Chinese hamster ovary cell expressing HXB2 envelope (K. Kozarsky, *et al.*, *J. Acquir. Immune. Defic. Syndr.*, *2*:163 (1989) and the HeLa-CD4-LTR-Beta-gal cells (M. Emerman, NIH AIDS Reagent program) in the presence of varying concentration of peptide. When mixed, these cells form syncytia, or multi-nucleated cells, which express β-galactosidase. Approximately twenty hours after co-culturing

the cells, the monolayers were stained with 5-bromo-4-chloro-3-indolyl-β-D-galactoside to visualize the syncytia. The syncytia are visualized with a microscope and counted manually (a syncytia is scored as a fused cell containing three or more nuclei). The IC_{50} was calculated from fitting the data to a Langmuir equation [$y = k/(1 + [peptide]/IC_{50}) + x$], where y = number of syncytia and k and x are scaling constants.

Table 1 Stability of mutant N36/C34 complexes and the inhibitory potency of C34 mutants.

Peptide	T_m (°C)	IC_{50} (nM) viral entry	IC_{50} (nM) cell fusion
Wildtype	66	2.1 ± 0.31	0.55 ± 0.03
Cavity-binding			
Trp^{628}→Ala	53	10 ± 2.0	3.8 ± 0.33
Trp^{631}→Ala	37	61 ± 16	15 ± 0.82
Ile^{635}→Ala	55	4.1 ± 0.91	0.96 ± 0.12
Control residues			
Met^{629}→Ala	66	2.0 ± 0.27	0.74 ± 0.03
Arg^{633}→Ala	65	2.6 ± 0.89	0.76 ± 0.07

Mutant C34 peptides (10 μM) were complexed with the N36 peptide (10 μM) in phosphate-buffered saline (pH 7.0) for circular dichroism (CD) measurements. The apparent melting temperatures (T_m) were estimated from the thermal dependence of the CD signal at 222 nm. Inhibition of viral entry was measured in a cell-culture infection assay using recombinant luciferase-expressing HIV-1. Inhibition of cell-cell fusion was measured in a syncytium assay. The

means and standard errors are from triplicate trials.

Similarly, the activity of the D-peptides described was assessed using the two assays described above. Results are shown in figures 6A-6B and 8A-8B.

Example 5: Crystallization of the IQ17/D10pep1 Complex and Ligand-Free IQN17

Peptide Purification, Crystallization

Peptides IQN17 and D10pep1 were synthesized by FMOC peptide chemistry, as described above.

A 10 mg/ml stock of a mixture of IQN17 and D10pep1 was prepared in water. The final concentration of IQN17 was about 1.37 nM, and the final concentration of D10pep1 was about 1.51 mM. Initial crystallization conditions were found using Crystal Kits I and II (Hampton Research), and then optimized. To grow the best diffracting crystals, one microliter of this stock was added to one microliter of the reservoir buffer (10% PEG 4000, 0.1 M NaCi pH 5.6, 20 % 2-propanol) and allowed to equilibrate against the reservoir buffer. Crystals belong to a space group P321 (a=b=41.83Å; c=84.82Å, $\alpha=\beta=90°$, $\gamma=120°$) and contain one IQN17/D10pep1 monomer in the asymmetric unit. A useful osmium derivative was produced by increasing the concentration of PEG 4000 in the reservoir solution by 4%, adding $(NH_4)_2OsCl_6$ to the reservoir solution to a final concentration of 5 mM and adding five microliters of the resulting solution to the drop containing the protein crystal. Prior to data collection native and heavy-atom derivative crystals were transferred into cryosolution containing 20% PEG 4000, 0.1 M NaCi PH 5.6, 20% 2-Propanol and flash-frozen using X-stream cryogenic crystal cooler (Molecular Structure Corporation).

The best diffracting crystals of ligand-free IQN17 were grown with a similar technique as above: on microliter of a 10 mg/ml solution of IQN17 in water was added to one microliter of the reservoir buffer (1.0 M K,Na Tartrate, 0.1 M NaHEPES pH 7.0) and allowed to equilibrate against the reservoir buffer. Before

flash freezing, the crystals were transferred into buffers consisting of the reservoir solution with increasing amounts of glycerol, up to a final concentration of 23% glycerol. Crystals belong to the space group $C222_1$ (a= 57.94 Å, b=121.96 Å, c= 73.67 Å; $\alpha=\beta=\gamma=90°$) and contain one IQN17 trimer in the asymmetric unit.

X-Ray Data Collection and Processing

Initial data were collected on a Rigaku RU300 rotating-anode x-ray generator mounted to an R-axis IV area detector (Molecular Structure Corporation). Diffraction data for IQN17 were collected at 100 K using a Quantum-4 CCD detector and the 5.0.2 beamline at the Advanced Light Source (Berkeley, USA). Final native and multiwavelength anomalous diffraction (MAD) data for IQN17/D10pep1 were collected at the Howard Hughes Medical Institute Beamline X4A at Brookhaven National Laboratory using a Raxis-IV detector. For MAD data, four wavelengths near the osmium L-III absorption edge were selected based on the fluorescence spectrum of the Os derivative crystal (Table 2). The four wavelengths were: 1.1398 Å, 1.1403 Å, 1.1393 Å, 1.1197 Å. Data sets were collected in 20° batches, allowing the same batch to be collected at each wavelength before moving to the next batch, in order to minimize the crystal decay between data sets. Reflections were integrated and scaled with the programs DENZO and SCALEPACK (Otwinowski, Z., (1993) in *Data Collection and Processing,* eds. Sawer, L., Isaacs, N. & Bailey, S. (SERC, Daresbury Laboratory, Warrington, England), pp. 55-62).

Further diffraction data processing, phase determination and map calculations were performed using the CCP4 suite of programs (*CCP4, Acta Cryst. D50*:760-763 (1994)). Intensities were reduced to amplitudes with the program TRUNCATE, and the data sets for the wavelengths closest to the Os L-III absorption edge ($\lambda1$, $\lambda2$, $\lambda3$) were scaled with SCALEIT to the remote wavelength ($\lambda4$) data set (Table 2).

Phase Determination and Crystallographic Refinement

Initially, phase determination for IQN17/D10pep1 crystals was attempted

with the molecular replacement technique using the theoretical model of IQN17 build from the published GCN4-pl$_Q$I and HIV gp41 structures (Eckert, D.M., *et al.* (1998) *J. Mol. Biol. 284*:859-865; Chan, D.C., *et al.* (1997) *Cell* 89, 263-273) with sidechains truncated to a polyserine chain. The resulting molecular replacement solutions were ambiguous and the electron density map did not reveal conformation of the D10pep1 peptide. The molecular replacement phases were good enough, however, for determining the coordinates of a single Os atom in the corresponding derivative using difference and anomalous fourier maps. The heavy atom binds on the cryallographic three-fold axis (0.333, 0.667, 0.047). MAD phases were then generated with the program MLPHARE (Table 2) and extended to higher resolution with the program DM. The quality of MAD electron density map at 1.5 Å resolution was exceptional, and revealed structural details of IQN17 and D10pep1 peptide with clarity. Electron density map interpretation and model building was done with the program O (Jones, T.A. *et al.* (1991) Acta Crystallogr. D47, 110-119). The structure of IQN17-D10pep1 complex was refined using the program CNS (Brünger, A.T. *et al., Acta Crystallogr. D54*, 905-921 (1998)). The correctness of the structure was checked with simulated annealing omit maps and with the program WHAT CHECK (Hoff, R.WW. *et al., Nature 381*: 272 (1996)). All residues of IQN17 and the D10pep1 peptide (when converted into its mirror image) occupy most preferred areas of the Ramachandran plot. The conformations of the majority of the residues are well defined except for the two most N-terminal residues of IQN17 and the side chains of Arg-6 and Arg-8 of the D10pep1 peptide.

The structure of ligand-free IQN17 was solved by molecular replacement using the program AMORE (Navaza, J. (1994) *Acta Crystallogr. A50*, 157-163) and the IQN17 part of the refined IQN17/D10pep1 structure as a test model. Three-fold noncrystallographic averaging, solvent flattening and histogram matching with the program DM was used for phase improvement. Electron density map interpretation and model building was done with the program O (Jones *et al., Acta Crystallogr. D54*, 905-921 (1991). The structure of the IQN17/D10pep1 complex was refined using the program CNS (Brunger, A.T. *et al., Acta Crystallogr. D54*, 905-921 (1998)).

The crystal structure can be used to design more effective and/or new D-peptides, peptidomemetics or other small molecules that inhibit HIV infectivity.

Example 6 Nuclear magnetic resonance (NMR) methods for identifying compounds which bind to the N-helix hydrophobic pocket of gp41

A. Assaying specific binding between the IQN17 hydrophobic pocket and D-peptides

NMR experiments were used to assay the binding of each D-peptide to IQN17. The single tryptophan residue of IQN17 (denoted Trp-571) provides an excellent probe of specific binding to the hydrophobic pocket of gp41. In deuterium oxide (deuterated water) buffers, the simple homonuclear one-dimensional ^{1}H NMR spectrum of IQN17 (Figure 9A, middle) shows five signals from the Trp-571 indole, extremely well-resolved from all other signals in the molecule. To test a compound for binding to the gp41 pocket, two one-dimensional ^{1}H NMR measurements were made on samples in deuterated buffers. First, a reference (control) spectrum of IQN17 was taken, identifying the Trp571 chemical shifts in the unbound form. A second spectrum was acquired on a sample containing both IQN17 and the compound in question. An optional third spectrum of the D-peptide (or other small molecule, or mix of molecules) was also taken. ^{1}H NMR experiments were performed on a Bruker AMX 500 spectrometer. Data was processed in Felix 98.0 (MSI) on Silicon Graphics computers, and all spectra were referenced to DSS. All experiments were performed at 25° C in 100 mM NaCl, 50 mM sodium phosphate (pH 7.5). All buffers used were >99.7% D_2O, to remove overlapping resonances from exchangeable backbone and side chain protons. Solute concentrations ranged from 0.3-1.0 mM for individual peptides, 0.8-1.0 mM for 1:1 commplexes of IQN17 with each D-peptide.

Simple binding of two or more components is expected to result both in broader peaks (due to the increased size of the complex) and in changes in chemical shifts (due to the different chemical environments experienced by nuclei in free and bound forms). Specific binding to the hydrophobic pocket is indicated by a change

in the Trp-571 chemical shifts, as well as by a broadening of peaks. Binding can also be indicated by similar changes in the chemical shifts and peak widths of the molecule (peptides and small organic molecules, for example) assayed. Figure 9A shows an example of these effects: the NMR spectrum of the IQN17/D10pep1a complex displays broader peaks and dramatically different chemical shifts than the spectra for either of the two separate components. All IQN17/D-peptide complexes studied gave similar results, though varying in the degree of chemical shift dispersion (Figure 9B). Thus, binding was indicated in all cases.

The x-ray crystallographic finding that the two conserved Trp residues, and the conserved Leu residue, in D10pep1 are directly involved in the binding of the IQN17 pocket, strongly suggests that these conserved residues participate in a similar manner when the other D-peptides bind the pocket. These conserved trypophan residues, and Trp-571 of IQN17, provide an opportunity to study the binding interfaces in greater detail. In the IQN17/D10pep1 crystal structure, the Trp-571 sidechain of IQN17 is in close contact with Trp-10 of D10pep1, with several protons of Trp-571 ($H_{\zeta 2}$, $H_{\eta 2}$, $H_{\zeta 3}$, $H_{\epsilon 3}$; the four scalar-coupled protons of the aromatic ring) above the plane of the Trp-10 indole group. In this position, aromatic ring current interactions (F.A. Bovey, *Nuclear Magnetic Resonance Spectroscopy* (1988)) are expected to alter the chemical shifts of some of those protons, moving peaks upfield in the manner seen (Figure 9A, bottom). Use of the structure-based chemical shift prediction program SHIFTS (version 3.0b2, K. Osapay, D. Sitkoff, D. Case) also predicted that only protons from Trp-571 will experience a large upfield shift, expecially the $H_{\zeta 3}$ proton. If the other D-peptides bind to the IQN17 pocket in the same fashion as D10pep1, a similar juxtaposition of Trp-571 and Trp-10 should occur, resulting in upfield-shifted peaks. All of the D-peptide/IQN17 complexes studied displayed such peaks, though varying in the extent of the shift (Figure 9B). The D10pep1 complex showed the most extreme upfield shifts, and the D10pep7a complex the least. The magnitude of these changes is very large, ranging from roughly 0.5 to 2 ppm for the most upfield-shifted proton ($H_{\zeta 3}$, in all cases where it could be assigned). In comparison, chemical shift differences often used to detect binding in SAR by NMR experiments (Shuker, S.B., Hajduk, P.J., Meadows, R.P.,

Fesik, S.W., *Science 274*:1531-1534 (1996)) are frequently in the range of 0.05 to 0.2 ppm.) Though a broad range of upfield chemical shifts was observed, ring-current effects can be highly sensitive to distance and orientation, so that small structural differences may give rise to substantial variations in chemical shift. (All of the upfield shifts observed are consistent with the approximate orientation of Trp side chains expected from the x-ray crystal structure.) Also, the upfield-shifted peaks are somewhat broadened compared to others in these NMR spectra (most likely due to some type of exchange process) an effect particularly pronounced for the complexes with D10pep5a and with D10pep7a.

To confirm that the strongly upfield-shifted peaks all correspond to a single sidechain (almost certainly Trp-571), two-dimensional NMR (TOCSY) experiments were performed on each of the IQN17/D-peptide complexes. As expected, the TOCSY experiments indicate that in each complex, the strongly upfield-shifted resonances all belong to the same aromatic side chain, identified as a group of four scalar-coupled protons. One example TOCSY spectrum is shown in Figure 9C. For several of the complexes studied, NOESY experiments also indicate contact between this sidechain and other (unassigned) aromatic groups, as expected from the IQN17/D10pep1 structure. Not all of the potential NOE crosspeaks could be resolved, due to intense spectral overlap in the 6.8-7.6 ppm region. 2D NOESY and TOCSY experiments as described in J. Cavanaugh, W.J. Fairbrother, A.G. Palmer, N.J. Skelton, *Protein NMR Spectroscopy: Principles and Practice* (1996) were performed on samples of IQN17 and of each complex, with mixing times ranging between 30-90 ms (NOESY) and 30-70 ms (TOCSY). Spectral widths of 11,111 Hz and 5555 Hz were used in the acquisition (t_2) and indirect (t_1) dimensions, respectively. TOCSY experiments employed the DIPSI-2rc mixing sequence (J. Cavanaugh, M. Rance, *J. Magn. Reson. Serv. A., 105*:328 (1993)).

We conclude that all D-peptides assayed clearly bind the hydrophobic pocket of IQN17. Additionally, in the majority of these IQN17 complexes (i.e., D10pep1, D10pep3, D10pep4, D10pep6, D10pep10, and D10pep12) the D-peptides contact the pocket with very similar binding interfaces, bringing Trp-571 in close contact with the aromatic ring of Trp-10. In the cases of complexes with D10pep5a and

D10pep7a this conclusion also seems very likely, although the more limited chemical shift dispersion and broader peaks raise a remote possibility of some other mode of binding.

The binding assay employed here can also be employed to assay binding of other molecules to the hydrophobic pocket of gp41 (e.g., such as found in IQN17). The assay is especially easy to interpret in a case where an aromatic group binds the pocket, as with the set of D-peptides described above. However, any pocket-binding molecules should also perturb the chemical shifts of Trp-571, an easily noticeable effect. In addition, new NMR signals generated by the small molecules themselves upon binding, are also indicative of binding.

The use of one-dimensional homonuclear ^{1}H NMR provides significant advantages over multidimensional heteronuclear NMR to determine specific binding: (1) Sensitivity is higher, allowing samples to be assayed more quickly; alternately the higher sensitivity makes possible the use of lower concentrations of IQN17 and of putative binding agents, allowing screening for higher-affinity compounds, and more of them simultaneously. (2) Non-isotopically labeled proteins are simpler to produce, and more cost-effective. However, two-dimensional NMR experiments, either homonuclear or heteronuclear (with ^{15}N and/or ^{13}C isotopic labeling) could also be employed.

B. Screening chemical libraries

The binding assay described in (A) above can be used to screen large numbers of compounds present in a chemical library. Simple one-dimensional homonuclear ^{1}H NMR experiments are sufficient to assess binding, with no requirement for isotopic labeling. Two-dimensional NMR experiments, either homonuclear or heteronuclear (with ^{15}N and/or ^{13}C isotopic labeling) could also be employed. Single compounds can be screened one at a time in this process. However, multiple compounds can also be combined in the same assay with IQN17 (or any representation of the gp41 N-helix coiled coil) and screened simultaneously. Binding to the pocket by any component of the mixture is indicated by a change in the Trp-571 chemical shifts. NMR signals from a large number of compounds together have the potential to obscure signals from Trp-571; these signals from

unbound molecules can be eliminated using pulsed field gradient techniques well known in the art. With use of these techniques and a commercially available NMR tube sample changer, the automated screening of large numbers of compounds is straightforward.

C. Evaluating the products of multiple combinatorial syntheses

The screening process described in (B) above can also be extended to take advantage of combinatorial organic synthetic methods. Such methods are currently being used to generate whole families of compounds, with each family containing a diverse number of chemically related compounds. By the simple assay described above, the products of an entire combinatorial synthesis can be screened simultaneously. If no binding is indicated, then there is no need to invest further attention in any member of that family of compounds. If binding is indicated, then a particular family of promising compounds can be targeted for more detailed investigation. Simple one-dimensional homonuclear ^{1}H NMR experiments are sufficient to assess binding, with no requirement for isotopic labeling. Two-dimensional NMR experiments, either homonuclear or heteronuclear (with ^{15}N and/or ^{13}C isotopic labeling) could also be employed.

Table 2. Data collection and refinement statistics

Data collection				
Crystal	λ (A)	Completeness (%)	R_{sym}[1] (%)	Resolution (A)
IQN17	1.0000	89.5	3.7	2.1
IQN17/D10	1.1197	93.8	4.8	1.5
Os λ1	1.1403	98.6	6.3	2.0
Os λ2	1.1399	96.8	9.7	2.0
Os λ3	1.1393	96.9	7.9	2.0
Os λ4	1.1197	97.0	8.4	2.0

MAD phasing statistics (22.0-2.0 A)								
Derivative	R_{iso}[2] (%)	R_{cullis}[3] Acentric	R_{cullis}[3] Centric	R_{cullis}[3] Anom.	Ph. Power[4] Acentric	Ph. Power[4] Centric	Occ.[5]	Anom. Occ.[5]
Os λ1 vs. λ4	7.3	0.75	0.61	0.47	1.41	1.21	-0.039	0.337
Os λ2 vs. λ4	5.2	0.83	0.71	0.44	1.04	1.15	-0.027	0.533
Os λ3 vs. λ4	3.3	0.97	0.97	0.49	0.35	0.28	-0.005	0.295

Overall figure of merit (before solvent flattening): 0.68

Refinement statistics									
Crystal	Non-hydrogen protein atoms	Waters	Ions	Resolution (Å)	Reflections total	R_{cryst}[6]	R_{free}[6]	R.m.s. deviations bonds (Å)	angles (°)
IQN17/D10	516	150	1	10.0 - 1.5	13549	0.214	0.245	0.012	1.498
IQN17	1143	160	1	5.0 - 2.5	7541	0.282	0.352	0.009	1.252

[1] $R_{sym} = \Sigma\Sigma_j|I_j-\langle I\rangle| / \Sigma\Sigma_j|\langle I\rangle|$, where I_j is the recorded intensity of the reflection j and $\langle I\rangle$ is the mean recorded intensity over multiple recordings.

[2] $R_{iso} = \Sigma||F_{(\lambda i)}| - |F_{(\lambda 4)}|| / \Sigma|F_{(\lambda 4)}|$, where $F_{(\lambda i)}$ is the structure factor at wavelength λi and $F_{(\lambda 4)}$ is the structure factor at the reference wavelength λ4.

[3] $R_{cullis} = \Sigma||F_{(\lambda i)}| \pm |F_{(\lambda 4)}| - |F_{h(\lambda i),c}|| / \Sigma|F_{(\lambda i)} \pm F_{(\lambda 4)}|$, where $F_{h(\lambda i),c}$ is the calculated heavy atom structure factor.

[4] Phase power = $\langle F_{h(\lambda i)}\rangle / E$, where $\langle F_{h(\lambda i)}\rangle$ is the root-mean-square heavy atom structure factor and E is the residual lack of closure error.

[5] Occupancies are values output from MLPHARE.

[6] $R_{cryst, free} = \Sigma||F_{obs}| - |F_{calc}|| / |F_{obs}|$, where the crystallographic and free R factors are calculated using the working and test sets, respectively. Test set contained 10% of reflections.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A peptide which comprises a soluble, trimeric form of a coiled-coil and a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV gp41.

2. The peptide of Claim 1 wherein the peptide is a D-peptide.

3. The D-peptide of Claim 2 wherein the coiled coil is selected from the group consisting of:
   (a) the coiled coil of GCN4-pI_QI;
   (b) the coiled coil of GCN4-pII;
   (c) the coiled coil of Moloney Murine Leukemia Virus; and
   (d) the coiled coil of ABC heterotrimer.

4. The D-peptide of Claim 3 wherein the amino acid sequence of the coiled coil is:
RMKQIEDKIEEIESKQKKIENEIARIKK (SEQ ID NO: 25).

5. The D-peptide of Claim 2 wherein the sufficient portion of the N peptide region of HIV gp41 comprises the sequence: LLQLTVWGIKQLQARIL (SEQ ID NO: 20).

6. The D-peptide of Claim 5 which is IQN17 (SEQ ID NO: 2).

7. A D-peptide which is a soluble, trimeric peptide model of the HIV gp41 hydrophobic pocket, wherein the D-peptide comprises SEQ ID NO: 25 and a sequence which comprises 17 amino acid residues, wherein the 17 amino

acid residues comprise the sequence: LLXLTVWGXKXLQXRXX (SEQ ID NO: 42), wherein L, T, V, W, G, K, Q and R are amino acid residues represented by the single letter amino acid code and X is any D-amino acid residue.

8. The D-peptide of Claim 7 wherein the sequence which comprises 17 amino acid residues is selected from the group consisting of: SEQ ID NO: 20; SEQ ID NO: 26; SEQ ID NO: 27 and SEQ ID NO: 42.

9. A D-peptide selected from the group consisting of:

(a) CDLKAKEWFWLC (SEQ ID NO: 3);
(b) CEARHREWAWLC (SEQ ID NO: 4);
(c) CELLGWEWAWLC (SEQ ID NO: 5);
(d) CLLRAPEWGWLC (SEQ ID NO: 6);
(e) CSRSQPEWEWLC (SEQ ID NO: 7);
(f) CGLGQEEWFWLC (SEQ ID NO: 8);
(g) CMRGEWEWSWLC (SEQ ID NO: 9);
(h) CPPLNKEWAWLC (SEQ ID NO: 10);
(i) CVLKAKEWFWLC (SEQ ID NO: 11);
(j) KKGACGLGQEEWFWLC (SEQ ID NO: 15);
(k) KKGACELLGWEWAWLC (SEQ ID NO: 16);
(l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);
(m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);
(n) KKGACPPLNKEWAWLC (SEQ ID NO: 19);
(o) a D-peptide comprising WXWL (SEQ ID NO: 23);
(p) a D-peptide comprising EWXWL (SEQ ID NO: 24);
(q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)
(r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
(r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
(t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);
(u) ac-GACGLGQEEWFWLCAA-am (SEQ ID NO: 44);

(v) ac-KKGACGLGQEEWFWLCAA-am (SEQ ID NO: 15);
(w) ac-KKKKGACGLGQEEWFWLCAA-am (SEQ ID NO: 45)
(x) ac-GACDLKAKEWFWLCAA-am (SEQ ID NO: 35);
(y) ac-KKGACDLKAKEWFWLCAA-am (SEQ ID NO: 39);
(z) ac-KKKKGACDLKAKEWFWLCAA-am (SEQ ID NO: 46);
(a') ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);
(b') ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);
(c') ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);
(d') ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);
(e') ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);
(f') ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);
(g') ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);
(h') ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);
(i') ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);
(j') ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);
(k') ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);
(l') ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);
(m') ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);
(n') ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);
(o') ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);
(p') ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);
(q') ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);
(r') ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);
(s') ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);
(t') ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);
(u') ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);
(v') ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);
(w') ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);
(x') ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and
(y') a variant of a sequence of (a) through (x'), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.

10. The peptide of Claim 1 wherein the peptide is an L-peptide.

11. The L-peptide of Claim 10 wherein the soluble, trimeric coiled-coil is selected from the group consisting of:

(a) the coiled coil of GCN4-pI$_Q$I;

(b) the coiled coil of GCN4-pII;

(c) the coiled coil of Moloney Murine Leukemia Virus; and

(d) the coiled coil of ABC heterotrimer.

12. The L-peptide of Claim 10 wherein the sufficient portion of the N peptide region of HIV gp41 comprises the sequence: LLQLTVWGIKQLQARIL (SEQ ID NO: 20).

13. The L-peptide of Claim 12 which is IQN17 (SEQ ID NO: 2).

14. An L-peptide which is a soluble, trimeric model of the HIV gp1 hydrophobic pocket, wherein the L-peptide comprises SEQ ID NO: 25 and a sequence which comprises 17 amino acid residues, wherein the 17 amino acid residues comprise the sequence: LLXLTVWGXKXLQXRXX, wherein L, T, V, W, G, K, Q and R are amino acid residues represented by the single letter amino acid code and X is any D-amino acid residue.

15. The L-peptide of Claim 14 wherein the sequence which comprises 17 amino acid residues is selected from the group consisting of: SEQ ID NO: 20; SEQ ID NO: 26; and SEQ ID NO: 27.

16. A method of identifying a drug that interferes with formation of a complex between C34 peptide and N36 peptide, comprising:

(a) combining a candidate drug to be assessed for its ability to interfere with formation of a complex between C34 peptide and N36 peptide, C34 peptide and N36 peptide, under conditions appropriate for

formatin of a complex between C34 peptide and N36 peptide, thereby forming a test sample; and

(b) determining whether formation of a complex between C34 peptide and N36 peptide is inhibited,

wherein if formation of the complex is inhibited, the candidate drug is a drug that interferes with formation of the complex whereby a drug that interferes with formation of the complex is identified.

17. The method of Claim 16 wherein a control sample is formed by combining C34 peptide and N36 peptide, under the same conditions as the conditions under which the test sample is formed in (a); formation of a complex between C34 peptide and N36 peptide is determined and the extent to which the complex is formed in the test sample is compared with the extent to which the complex is formed in the control sample, wherein if the complex is formed to a lesser extent in the test sample than in the control sample, the candidate drug is a drug that interferes with formation of the complex, whereby a drug that interferes with formation of the complex is identified.

18. The method of Claim 16 wherein C34 peptide and N36 peptide are each labeled by a member of a pair of donor-acceptor molecules and the extent to which formation of a complex between C34 and N36 occurs is assessed by determining the extent to which light emission occurs from the acceptor molecule, wherein if light emission occurs to a lesser extent in the presence of the candidate drug than in the absence of the candidate drug, the candidate drug is a drug that interferes with formation of a complex between C34 peptide and N36 peptide.

19. The method of Claim 17 wherein C34 peptide and N36 peptide are each labeled by a member of a pair or donor-acceptor molecules and the extent to which light emission occurs is assessed in the test sample and in the control sample, wherein if light emission is less in the test sample than in the control

sample, the candidate drug is a drug which inhibits formation of a complex between C34 prptide and N36 peptide.

20. The method of Claim 16 further comprising assessing whether the drug that interferes with formation of the complex is an inhibitor of HIV entry into cells by assessing the effect of the drug on cell/cell fusion or HIV infection of cells is less in the presence of the drug than in its absence, the drug is an inhibitor of HIV entry into cells.

21. A method of eliciting an immune response in an individual, comprising introducing into the individual a peptide comprising a trimeric form of a coiled-coil region of a protein and a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form part or all of the N-helix coiled-coil of HIV gp41 and the peptide is present in a pharmaceutically acceptable carrier.

22. The method of Claim 21 wherein the peptide is introduced into the individual by a route of administration selected from the group consisting of: intramuscularly, intraperitoneally, orally, nasally and transdermally.

23. The method of Claim 21 wherein the coiled-coil is selected from the group consisting of: GCN4-pI$_Q$I; GCN4-pII; Moloney Murine Leukemia Virus and ABC heterotrimer.

24. The method of Claim 21 wherein the peptide is IQN17.

25. A method of interfering with entry of HIV into a mucosal cell comprising administering or applying to a mucosal surface a composition comprising: (1) a drug which binds HIV envelope protein gp41 subunit and interferes with entry of HIV into cells of the mucosal surface and (2) a carrier or base.

26. The method of Claim 25 wherein the drug binds the cavity on the surface of the N-helix coiled-coil of HIV envelope protein gp41 subunit.

27. The method of Claim 26 wherein the drug prevents or reduces the gp41 conformational change, thereby interfering with entry of HIV into cells of the mucosal surface.

28. The method of Claim 25 wherein the composition comprises a component selected from the group consisting of:

(a) C34 peptide;
(b) DP178;
(c) DP649;
(d) T1249;
(e) a derivative of (a) - (d);
(f) a D-peptide which binds to the hydrophobic pocket of HIV gp41;
(g) a derivative of (f);
(h) a combination of two or more of (a)-(g); and
(i) a molecule that inhibits HIV infectivity by binding to the N-helix coiled coil.

29. The method of Claim 28 wherein the carrier or base is selected from the group consisting of: a foam, a gel, other substance sufficiently viscous to retain the drug, water and a buffer.

30. The method of Claim 28 wherein the carrier or base is a vaginal suppository or rectal suppository.

31. The method of Claim 28 wherein the drug is released from the carrier or base immediately or soon after it is administered or applied to the vagina, mouth or rectum.

32. The method of Claim 28 wherein the drug is released from the carrier or base gradually or after a specified period after it is administered or applied to the vagina, mouth or rectum.

33. The method of Claim 28 wherein the drug is on the surface of or incorporated within a contraceptive device in a manner which permits release of the drug under conditions of use.

34. The method of Claim 28 wherein the D-peptide of (e) comprises an amino acid sequence selected from the group consisting of:

(a) CDLKAKEWFWLC (SEQ ID NO: 3);
(b) CEARHREWAWLC (SEQ ID NO: 4);
(c) CELLGWEWAWLC (SEQ ID NO: 5);
(d) CLLRAPEWGWLC (SEQ ID NO: 6);
(e) CSRSQPEWEWLC (SEQ ID NO: 7);
(f) CGLGQEEWFWLC (SEQ ID NO: 8);
(g) CMRGEWEWSWLC (SEQ ID NO: 9);
(h) CPPLNKEWAWLC (SEQ ID NO: 10);
(i) CVLKAKEWFWLC (SEQ ID NO: 11);
(j) KKGACGLGQEEWFWLC (SEQ ID NO: 15);
(k) KKGACELLGWEWAWLC (SEQ ID NO: 16);
(l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);
(m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);
(n) KKGACPPLNKEWAWLC (SEQ ID NO: 19);
(o) a D-peptide comprising WXWL (SEQ ID NO: 23);
(p) a D-peptide comprising EWXWL (SEQ ID NO: 24);
(q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)
(r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
(r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
(t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);
(u) ac-GACGLGQEEWFWLCAA-am (SEQ ID NO: 44);

(v) ac-KKGACGLGQEEWFWLCAA-am (SEQ ID NO: 15);

(w) ac-KKKKGACGLGQEEWFWLCAA-am (SEQ ID NO: 45)

(x) ac-GACDLKAKEWFWLCAA-am (SEQ ID NO: 35);

(y) ac-KKGACDLKAKEWFWLCAA-am (SEQ ID NO: 39);

(z) ac-KKKKGACDLKAKEWFWLCAA-am (SEQ ID NO: 46);

(a′) ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);

(b′) ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);

(c′) ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);

(d′) ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);

(e′) ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);

(f′) ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);

(g′) ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);

(h′) ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);

(i′) ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);

(j′) ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);

(k′) ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);

(l′) ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);

(m′) ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);

(n′) ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);

(o′) ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);

(p′) ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);

(q′) ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);

(r′) ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);

(s′) ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);

(t′) ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);

(u′) ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);

(v′) ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);

(w′) ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);

(x′) ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and

(y′) a variant of a sequence of (a) through (x′), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.

35. A method of identifying a compound or molecule which binds the N-helix coiled-coil cavity of HIV-1 gp41 envelope protein, wherein the compound or molecule to be assessed is referred to as a candidate inhibitor, comprising:

(a) combining a D-peptide which binds the N-helix coiled-coil cavity, a fusion protein which is a soluble model which presents the N-helix coiled-coil cavity and a candidate inhibitor, under conditions appropriate for binding of the D-peptide to the N-helix coiled-coil cavity, thereby producing a test sample;

(b) determining the extent to which binding of the D-peptide to the N-helix coiled-coil cavity in the test sample; and

(c) comparing the extent of binding determined in to the N-helix coiled-coil cavity in a control sample, wherein the control sample is the same as the test sample except that the control sample does not include the candidate inhibitor and is maintained under the same conditions appropriate for binding of the D-peptide to the N-helix coiled-coil cavity as is the test sample,

wherein if the extent of binding in the test sample is less than the extent of binding in the control sample, the candidate inhibitor is a compound or molecule which binds the N-helix coiled-coil cavity of HIV-1 gp41 envelope protein.

36. The method of Claim 35 wherein the fusion protein is IQN17.

37. The method of Claim 35 wherein the D-peptide is labeled with a fluorescent reporter and the fusion protein is labeled with a quencher which, when in sufficiently close proximity to the fluorescent reporter, quenches the signal from the reporter and detection of a signal from the fluorescent reporter indicates that the candidate inhibitor is a compound or molecule which binds the N-helix coiled-coil cavity of HIV-1 gp41 envelope protein.

38. A fusion protein comprising a trimeric form of the coiled-coil region of

GCN4 and a portion of the N-peptide region of HIV-1 gp41, wherein the portion of the N-peptide region of gp41 comprises part or all or none of the N-helix coiled-coil pocket of HIV-1 gp41.

39. A fusion protein of Claim 38 wherein the portion of the N-peptide region of HIV gp41 comprises the following 24 amino acid residues of HIV: SGIVQQQNNLLRAI EAQQHLLQLT.

40. A method of eliciting an immune response in an individual, comprising introducing into the individual a fusion protein comprising a soluble, trimeric form of a coiled-coil and a sufficient portion of the N-peptide region of HIV-1 gp41, to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV-1 gp41, wherein the fusion protein is present in a pharmaceutically acceptable carrier.

41. A D-peptide which comprises at least four amino acid residues and comprises the consensus sequence WXWL, wherein W represents D-tryptophan, L represents D-leucine and X represents any moiety.

42. The D-peptide of laim 41 wherein X is a D-amino acid residue or a modified D-amino acid residue.

43. The D-peptide of Claim 41, wherein the D-peptide comprises 2 to 21 amino acid residues.

44. A D-peptide which comprises at least five amino acid residues, wherein the at least five amino acid residues are EWXWL, wherein E represents D-glutamic acid, W represents D-tryptophan, L represents D-leucine and X represents an amino acid residue, a modified amino acid residue or a moiety other than an amino acid residue.

45. A D-peptide which comprises an amino acid sequence selected from the group consisting of:

(a) CDLKAKEWFWLC (SEQ ID NO: 3);

(b) CEARHREWAWLC (SEQ ID NO: 4);

(c) CELLGWEWAWLC (SEQ ID NO: 5);

(d) CLLRAPEWGWLC (SEQ ID NO: 6);

(e) CSRSQPEWEWLC (SEQ ID NO: 7);

(f) CGLGQEEWFWLC (SEQ ID NO: 8);

(g) CMRGEWEWSWLC (SEQ ID NO: 9);

(h) CPPLNKEWAWLC (SEQ ID NO: 10);

(i) CVLKAKEWFWLC (SEQ ID NO: 11);

(j) KKGACGLGQEEWFWLC (SEQ ID NO: 15);

(k) KKGACELLGWEWAWLC (SEQ ID NO: 16);

(l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);

(m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);

(n) KKGACPPLNKEWAWLC (SEQ ID NO: 19);

(o) a D-peptide comprising WXWL (SEQ ID NO: 23);

(p) a D-peptide comprising EWXWL (SEQ ID NO: 24);

(q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)

(r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);

(r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);

(t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);

(u) ac-GACGLGQEEWFWLCAA-am (SEQ ID NO: 44);

(v) ac-KKGACGLGQEEWFWLCAA-am (SEQ ID NO: 15);

(w) ac-KKKKGACGLGQEEWFWLCAA-am (SEQ ID NO: 45)

(x) ac-GACDLKAKEWFWLCAA-am (SEQ ID NO: 35);

(y) ac-KKGACDLKAKEWFWLCAA-am (SEQ ID NO: 39);

(z) ac-KKKKGACDLKAKEWFWLCAA-am (SEQ ID NO: 46);

(a') ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);

(b') ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);

(c') ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);

(d′) ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);

(e′) ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);

(f′) ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);

(g′) ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);

(h′) ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);

(i′) ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);

(j′) ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);

(k′) ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);

(l′) ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);

(m′) ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);

(n′) ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);

(o′) ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);

(p′) ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);

(q′) ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);

(r′) ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);

(s′) ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);

(t′) ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);

(u′) ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);

(v′) ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);

(w′) ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);

(x′) ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and

(y′) a variant of a sequence of (a) through (x′), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.

46. A method of identifying a drug that binds the N-helix coiled-coil cavity of HIV gp41 comprising:

(a) combining: (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIVgp41 and; (2) a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to

include the HIV gp41 cavity, under conditions appropriate for presentation of the HIV gp41 cavity for binding by a drug; and

(b) determining whether the candidate drug binds the HIV gp41 cavity, wherein if binding occurs, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41.

47. The method of Claim 46 wherein in (a), a peptide which binds the N-helix coiled-coil cavity of HIV gp41 is combined with the candidate drug and the fusion protein and in (b), whether the candidate drug binds the HIV gp41 cavity is determined in the presence of the peptide which binds the N-helix coiled-coil cavity of HIV gp41.

48. The method of Claim 42 wherein the peptide which binds the N-helix coiled-coil cavity of HIV gp41 is selected from the group consisting of:

(a) CDLKAKEWFWLC (SEQ ID NO: 3);
(b) CEARHREWAWLC (SEQ ID NO: 4);
(c) CELLGWEWAWLC (SEQ ID NO: 5);
(d) CLLRAPEWGWLC (SEQ ID NO: 6);
(e) CSRSQPEWEWLC (SEQ ID NO: 7);
(f) CGLGQEEWFWLC (SEQ ID NO: 8);
(g) CMRGEWEWSWLC (SEQ ID NO: 9);
(h) CPPLNKEWAWLC (SEQ ID NO: 10);
(i) CVLKAKEWFWLC (SEQ ID NO: 11);
(j) KKGACGLGQEEWFWLC (SEQ ID NO: 15);
(k) KKGACELLGWEWAWLC (SEQ ID NO: 16);
(l) KKKKGACELLGWEWAWLC (SEQ ID NO: 17);
(m) KKGACMRGEWEWSWLC (SEQ ID NO: 18);
(n) KKGACPPLNKEWAWLC (SEQ ID NO: 19);
(o) a D-peptide comprising WXWL (SEQ ID NO: 23);
(p) a D-peptide comprising EWXWL (SEQ ID NO: 24);
(q) a D-peptide comprising CXXXXXEWXWL (SEQ ID NO: 12)

(r) ac-GACEARHREWAWLCAA-am (SEQ ID NO: 34);
(r) ac-KKGACEARHREWAWLCAA-am (SEQ ID NO: 38);
(t) ac-KKKKGACEARHREWAWLCAA-am (SEQ ID NO: 43);
(u) ac-GACGLGQEEWFWLCAA-am (SEQ ID NO: 44);
(v) ac-KKGACGLGQEEWFWLCAA-am (SEQ ID NO: 15);
(w) ac-KKKKGACGLGQEEWFWLCAA-am (SEQ ID NO: 45)
(x) ac-GACDLKAKEWFWLCAA-am (SEQ ID NO: 35);
(y) ac-KKGACDLKAKEWFWLCAA-am (SEQ ID NO: 39);
(z) ac-KKKKGACDLKAKEWFWLCAA-am (SEQ ID NO: 46);
(a′) ac-GACELLGWEWAWLCC-am (SEQ ID NO: 47);
(b′) ac-KKGACELLGWEWAWLCAA-am (SEQ ID NO: 16);
(c′) ac-KKKKGACELLGWEWAWLCAA-am (SEQ ID NO: 17);
(d′) ac-GACSRSQPEWEWLCAA-am (SEQ ID NO: 36);
(e′) ac-KKGACSRSQPEWEWLCAA-am (SEQ ID NO: 40);
(f′) ac-KKKKGACSRSQPEWEWLCAA-am (SEQ ID NO: 48);
(g′) ac-GACLLRAPEWGWLCAA-am (SEQ ID NO: 37);
(h′) ac-KKGACLLRAPEWGWLCAA-am (SEQ ID NO: 41);
(i′) ac-KKKKGACLLRAPEWGWLCAA-am (SEQ ID NO: 49);
(j′) ac-GACMRGEWEWSWLCAA-am (SEQ ID NO: 50);
(k′) ac-KKGACMRGEWEWSWLCAA-am (SEQ ID NO: 18);
(l′) ac-KKKKGACMRGEWEWSWLCAA-am (SEQ ID NO: 51);
(m′) ac-GACPPLNKEWAWLCAA-am (SEQ ID NO: 52);
(n′) ac-KKGACPPLNKEWAWLCAA-am (SEQ ID NO: 19);
(o′) ac-KKKKGACPPLNKEWAWLCAA-am (SEQ ID NO: 53);
(p′) ac-GACXXXXXEWXWLCAA-am (SEQ ID NO: 54);
(q′) ac-KKGACXXXXXEWXWLCAA-am (SEQ ID NO: 55);
(r′) ac-KKKKGACXXXXXEWXWLCAA-am (SEQ ID NO: 56);
(s′) ac-XXCXXXXXEWXWLCXX-am (SEQ ID NO: 57);
(t′) ac-KKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 58);
(u′) ac-KKKKXXCXXXXXEWXWLCXX-am (SEQ ID NO: 59);
(v′) ac-XXCXXXXXEWXWLCXXX-am (SEQ ID NO: 60);

(w') ac-KKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 61);

(x') ac-KKKKXXCXXXXXEWXWLCXXX-am (SEQ ID NO: 62); and

(y') a variant of a sequence of (a) through (x'), wherein the variant binds the N-helix coiled-coil cavity of HIV gp41, wherein ac- at the C-terminus and -am at the N-terminus are optional.

49. The method of Claim 46 wherein the candidate drug is detectably labeled and binding of the candidate drug to the HIV gp41 cavity is determined by detecting the presence of the detectable label on the HIV gp41 cavity.

50. The method of Claim 46 wherein the fusion protein comprises a soluble, trimeric version of the coiled-coil region of GCN4 and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity.

51. The method of Claim 50 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO.: 2.

52. A method of identifying a drug that binds the N-helix coiled-coil cavity of HIV gp41 comprising:

(a) combining: (1) a soluble model that presents the N-helix coiled-coil cavity of HIV gp 41 in such a manner that it is available for binding by a drug and (2) a candidate drug, which is to be assessed for its ability to bind the N-helix coiled-coil cavity; and

(b) determining whether the candidate drug binds the N-helix coiled coil cavity of the soluble model,

wherein if binding occurs, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41.

53. A method of producing a drug that binds the N-helix coiled-coil cavity of HIV gp41 and inhibits HIV entry into cells, comprising

(a) combining (1) a candidate drug to be assessed for its ability to bind

the N-helix coiled-coil cavity of HIV gp41 and inhibit HIV entry into cells and (2) a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity, under conditions appropriate for presentation of the HIV gp41 cavity for binding by a drug;

(b) determining whether the candidate drug binds the HIV gp41 cavity, wherein if binding of the candidate drug to the N-helix coiled-coil cavity of HIV gp41, occurs, the candidate *drug* is a drug which binds the N-helix coiled-coil cavity of HIV gp41, whereby a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced; and

(c) assessing the ability of the drug produced in (b) to inhibit HIV entry into cells, wherein if the drug inhibits HIV entry into cells, it is a drug which binds the N-helix coiled-coil cavity of HIV gp41 and inhibits HIV entry into cells.

54. The method of Claim 53 wherein the fusion protein of (a)(2) comprises a soluble, trimeric coiled-coil region of GCN4 and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity and the ability of the drug produced in (b) to inhibit HIV entry into cells is assessed in a syncytium assay, an infection assay or both.

55. The method of Claim 54 wherein the drug identified in (c) is further assessed for its ability to inhibit HIV entry into cells by *in vivo* assessment in an appropriate animal model.

56. The method of Claim 54 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO.:2.

57. A method of producing a soluble model of the N-helix coiled-coil cavity of HIV gp41, comprising producing a fusion protein comprising: (a) a soluble,

trimeric form of a coiled-coil and (b) a sufficient portion of the N-peptide region of HIV gp41 to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV gp41.

58. The method of Claim 57 wherein the protein of (a) is GCN4-pI$_Q$I, GCN4-pII, Moloney Murine Leukemia Virus or ABC heterotrimer and the sufficient portion of (b) is selected from the group consisting of a portion comprising SEQ ID NO: 20; a portion comprising SEQ ID NO: 26; a portion comprising SEQ ID NO: 27 and a portion comprising SEQ ID NO: 42.

59. The method of Claim 57 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO: 2.

60. A method of producing a drug that binds the N-helix coiled-coil cavity of HIV gp41 comprising,

(a) producing or obtaining a soluble model of the N-helix coiled-coil cavity of HIV gp41;

(b) combining: (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 and (2) the soluble model of the N-helix coiled-coil cavity of HIV gp41; and

(c) determining whether the candidate drug binds the N-helix coiled-coil cavity of HIV gp41,

wherein if the candidate drug binds the N-helix coiled-coil cavity of HIV gp41, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41,whereby a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced.

61. The method of Claim 60 wherein the soluble model is a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity.

62. The method of Claim 61 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID NO.:2.

63. A method of producing a drug that binds the N-helix coiled-coil cavity of HIV gp41 and inhibits its entry into cells, comprising;

(a) producing or obtaining a soluble model of the N-helix coiled-coil cavity of HIV gp41;

(b) combining: (1) a candidate drug to be assessed for its ability to bind the N-helix coiled-coil cavity of HIV gp41 and (2) the soluble model of the N-helix coiled-coil cavity of HIV gp41;

(c) determining whether the candidate drug binds the N-helix coiled-coil cavity of HIV gp41, wherein if the candidate drug binds the N-helix coiled-coil cavity of HIV gp41, the candidate drug is a drug which binds the N-helix coiled-coil cavity of HIV gp41, whereby a drug which binds the N-helix coiled-coil cavity of HIV gp41 is produced and;

(d) assessing the ability of the drug produced in (c) to inhibit HIV entry into cells,

wherein if the drug inhibits HIV entry into cells, it is a drug which binds the N-helix coiled-coil cavity of HIV gp41 and inhibits HIV entry into cells.

64. The method of Claim 63 wherein the soluble model is a fusion protein which comprises a trimeric version of the coiled-coil region of a protein and a sufficient portion of the N-peptide of HIV gp41 to include the HIV gp41 cavity.

65. The method of Claim 64 wherein the fusion protein is IQN17 or a variant thereof, wherein the amino acid sequence of IQN17 is SEQ ID No.;2.

66. A drug produced by the method of Claim 60.

67. A drug produced by the method of Claim 61.

68. A drug produced by the method of Claim 62.

69. A drug produced by the method of Claim 63.

70. A drug produced by the method of Claim 64.

71. A drug produced by the method of Claim 65.

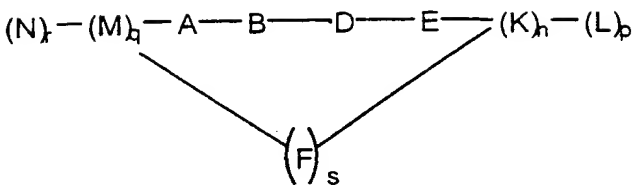
72. A method of identifying a peptide that binds to the N-helix coiled-coil cavity of HIV gp41, comprising:

(a) combining IQN17 in the D-handedness with a phage display library of L-amino acid peptides, under conditions appropriate for binding of members of the library to IQN17 in the D-handedness; and

(b) determining if binding occurs between IQN17 in the D-handedness and a member or members of the phage display library, wherein if binding occurs, a peptide that binds to the N-helix coiled-coil cavity of HIV gp41 in the D-handedness is identified.

73. The method of Claim 72 further comprising determining the amino acid sequence of the member or members of the phage display library which bind to IQN17 in the D-handedness and producing peptides, in D form, comprising the amino acid sequences determined, wherein the peptides in D form bind the N-helix coiled-coil cavity in the natural L-handedness.

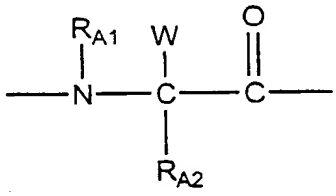
74. A compound of Formula I,



(I),

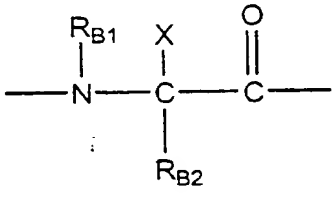
wherein

A is a D- amino acid residue or an N-substituted glycyl residue of the formula



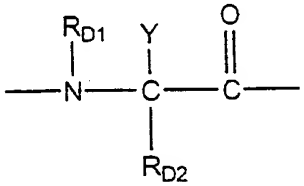
wherein one of R_{A1} and R_{A2} is a substituted or unsubstituted aryl, heteroaryl, arylmethyl, heteroarylmethyl, benzo-fused aryl, benzo-fused heteroaryl, benzo-fused arylmethyl, benzo-fused heteroarylmethyl, cycloalkyl or bicycloalkyl; and the other is hydrogen; and W is hydrogen, methyl, trifluoromethyl or halogen, for example, fluorine, chlorine, bromine or iodine;

B is a glycyl residue or a D-amino acid or N-substituted glycyl residue of the formula



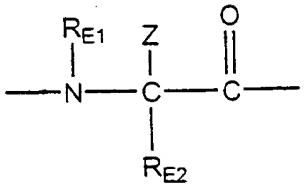
wherein one of R_{B1} and R_{B2} is a substituted or unsubstituted linear, branched or cyclic alkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl group; and the other is hydrogen; and X is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine;

D is a D- amino acid residue or N-substituted glycyl residue of the formula



wherein one of R_{D1} and R_{D2} is a substituted or unsubstituted aryl, heteroaryl, arylmethyl, heteroarylmethyl, benzo-fused aryl, benzo-fused heteroaryl, benzo-fused arylmethyl; benzo-fused heteroarylmethyl, cycloalkyl or bicycloalkyl; and the other is hydrogen; andY is hydrogen, methyl, trifluoromethyl or halogen, such as fluorine, chlorine, bromine or iodine;

E is a D-amino acid residue or N-substituted glycyl residue of the formula



wherein one of R_{E1} and R_{E2} is a substituted or unsubstituted, linear, branched or cyclic alkyl, aryl or arylalkyl group; and the other is hydrogen; and Z is hydrogen, methyl, trifluoromethyl or halogen,

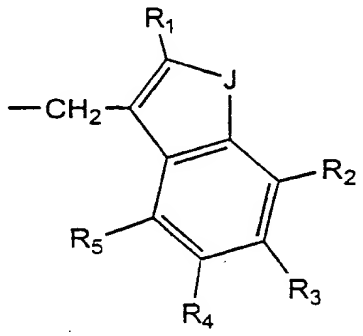
such as fluorine, chlorine, bromine or iodine;

K, L, M and N are each, independently, an amino acid residue or a polypeptide group comprising 2 to about 8 amino acid residues;

F is a direct bond or a difunctional linking group; and

n, p, q, r and s are each, independently, 0 or 1.

75. The compound of Claim 74 wherein one of R_{A1} and R_{A2} and one of R_{D1} and R_{D2} are, independently, a phenyl, substituted phenyl, naphthyl, substituted naphthyl, naphthylmethyl, substituted naphthylmethyl, benzyl or substituted benzyl group, or a group of the formula



where J is O, S or NR, where R is H or linear, branched or cyclic C_1-C_6-alkyl; and

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of

hydrogen, halogen and alkyl.

76. The compound of Claim 75 wherein R_{A1} and R_{D1} are both hydrogen.

77. The compound of Claim 74 wherein one of R_{B1} and R_{B2} is hydrogen, substituted or unsubstituted linear, branched or cyclic C_1-C_4-alkyl, phenyl, benzyl, naphthyl or naphthylmethyl.

78. The compound of Claim 77 wherein R_{B1} is hydrogen.

79. The compound of Claim 74 wherein one of R_{E1} and R_{E2} is a substituted or unsubstituted, linear, branched or cyclic C_1-C_6-alkyl group or a substituted or unsubstituted phenyl or naphthyl group and the other is hydrogen.

80. The compound of Claim 79 wherein R_{E1} is hydrogen.

81. The compound of Claim 74 wherein A and D are each a D-tryptophan residue and E is a D-leucine residue.

82. The compound of Claim 74 wherein K is a D-amino acid residue or an N-substituted glycyl residue comprising an amino-, carboxyl- or sulfhydryl substituted side chain and L is a polypeptide comprising 2 or 3 D-amino acid residues or N-substituted glycine residues.

83. The compound of Claim 74 wherein M is a polypeptide group comprising from 2 to about 8 D-amino acid residues, of which at least one comprises an amino-, carboxy- or sulfhydryl substituted side chain, and N is a polypeptide group comprising from 1 to about 6 amino acid residues, of which at least one is a lysine residue.

84. The compound of Claim 74 wherein F is a divalent linking group having a length from about 2 to about 40 atoms.

85. The compound of Claim 84 wherein F is a polypeptide linking group of the formula $-P_n-$, wherein n is an integer from 1 to about 12 and each P is

independently an L- or D- amino acid or N-substituted glycyl residue, a glycyl residue or an N-substituted glycyl residue.

86. The compound of Claim 84 wherein F is a substituted or unsubstituted C_4-C_{40}-alkylene group or a C_4-C_{40}-alkylene group which is interrupted at one or more points by a heteroatom, a phenylene group or a heteroarylene group.

87. The compound of Claim 84 wherein F is a polysaccharide group comprising from 1 to about 10 glycoside groups.

88. A method of producing a drug which fits the N-helix coiled-coil pocket of HIV gp41, comprising:

(a) obtaining a crystal of a soluble, trimeric peptide model of the HIV gp41 hydrophobic pocket;

(b) obtaining the atomic coordinates of the peptide model by X-ray diffraction studies using the crystal obtained in (a);

(c) using the atomic coordinates obtained in (b) to define the N-helix coiled-coil pocket of HIV gp41;

(d) identifying a molecule or compound which fits the N-helix coiled-coil pocket of HIV gp41;

(e) obtaining the molecule or compound identified in (d); and

(f) contacting the molecule or compound obtained in (e) with the N-helix coiled-coil pocket of HIV gp41 to assess the ability of the molecule or compound to fit the pocket of HIV gp41;

wherein if the molecule or compound fits the N-helix coiled-coil pocket of HIV gp41, the molecule or compound is a drug which fits the pocket, whereby a drug which fits the N-helix coiled-coil pocket of HIV gp41 is produced.

89. The method of Claim 88 wherein the soluble, trimeric peptide molecule comprises a soluble, trimeric form of a coiled coil and a sufficient portion of

the N-peptide region of HIV gp41 to comprise the amino acid residues which form the pocket of the N-helix coiled-coil of HIV gp41.

90. The method of Claim 89 wherein in (f), the molecule or compound is contacted with the N-helix coiled-coil pocket of HIV gp41 by contacting the molecule or compound with IQN17, the N-helix of HIV gp41 or a polypeptide which comprises the HIV pocket.

91. The method of Claim 89 wherein the soluble model is IQN17.

92. The method of Claim 88 wherein the crystal obtained in (a) is a crystal of IQN17 of space group C222.

93. A method of producing a drug which binds the N-helix coiled-coil pocket of HIV gp41, comprising:

(a) obtaining the atomic coordinates of IQN17;

(b) using the atomic coordinates obtained in (a) to define the N-helix coiled-coil pocket of HIV gp41;

(c) identifying a molecule or compound which fits the N-helix coiled-coil pocket of HIV gp41;

(d) obtaining the molecule or compound identified in (c); and

(e) contacting the molecule or compound obtained in (d) with the N-helix coiled-coil pocket of HIV gp41 to assess the ability of the molecule or compound to fit the pocket of HIV gp41,

wherein if the molecule or compound fits the N-helix coiled-coil pocket of HIV gp41, the molecule or compound is a drug which fits the pocket, whereby a drug which fits the N-helix coiled-coil pocket of HIV gp41 is produced.

94. The method of Claim 93 wherein the atomic coordinates are the atomic coordinates in the PDB file represented in Figures 11A-11V.

95. A method of identifying a molecule that binds to the N-helix coiled-coil cavity of HIV gp41, comprising:

(a) combining IQN17 in the D-handedness with a biologically encoded library of ligands, under conditions appropriate for binding of members of the library to IQN17 in the D-handedness; and

(b) determining if binding occurs between IQN17 in the D-handedness and a member or members of the biologically encoded library, wherein if binding occurs, a ligand that binds to the N-helix coiled-coil cavity of HIV gp41 in the D-handedness is identified.

96. The method of Claim 95 further comprising determining the sequence of the member or members of the biologically encoded library which bind to IQN17 in the D-handedness, and producing ligands, in the mirror-image handedness of the biologically encoded ligands, comprising the sequences determined.

97. The method of Claim 95 wherein the biologically encoded library is selected from the group consisting of a phage display library, a DNA library, an RNA library and a biologically encoded peptide library.

Figure 1

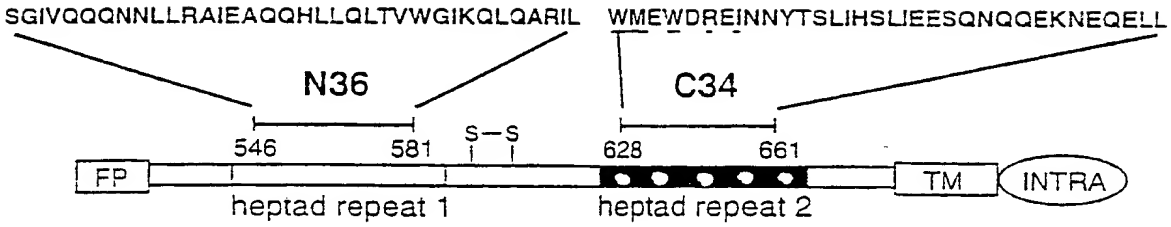

SGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARIL
WMEWDREINNYTSLIHSLIEESQNQQEKNEQELL
N36
C34
546
581
S—S
628
661
FP
TM
INTRA
heptad repeat 1
heptad repeat 2

Figure 2: Correlation of C34 Inhibitory Potency With N36/C34 Stability

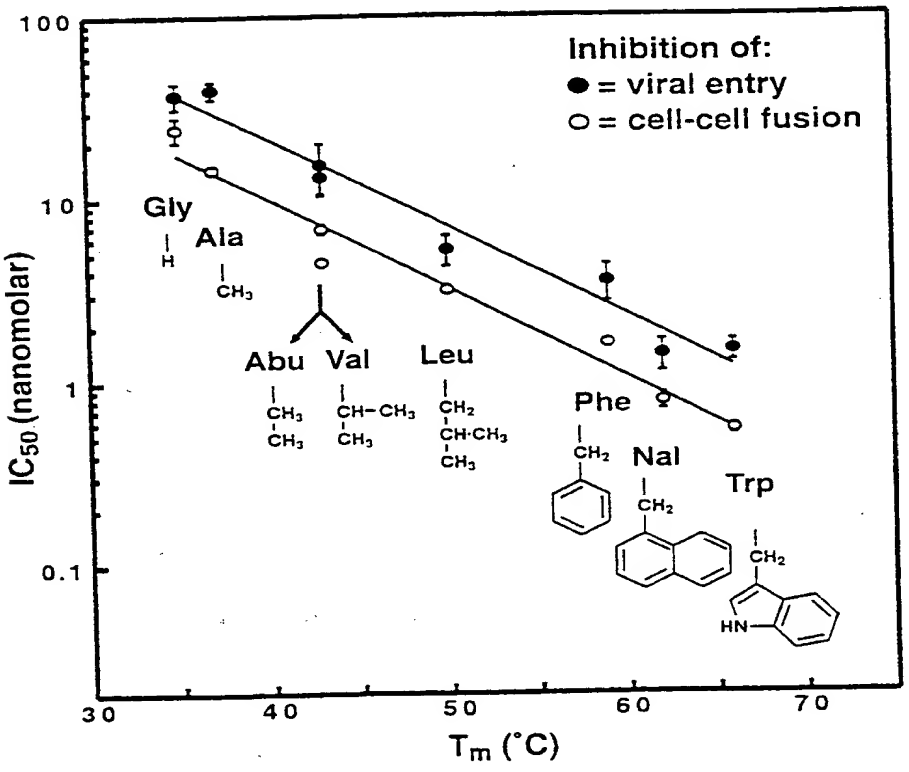


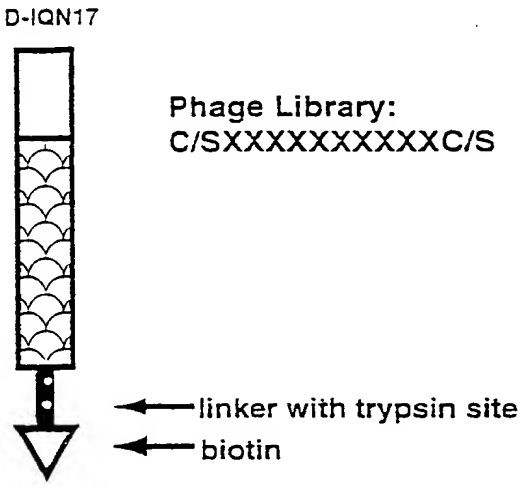
Figure 3: D-peptide Sequences

D10pep1 :	Ac- G A C E A R H R E W A W L C A A - CONH2
D10pep1a:	Ac - KK G A C E A R H R E W A W L C A A - CONH2
D10pep3 :	Ac - KK G A C G L G Q E E W F W L C A A - CONH2
D10pep4 :	Ac - G A C D L K A K E W F W L C A A - CONH2
D10pep5 :	Ac - KK G A C E L L G W E W A W L C A A - CONH2
D10pep5a:	Ac - KKKK G A C E L L G W E W A W L C A A - CONH2
D10pep6 :	Ac - G A C S R S Q P E W E W L C A A - CONH2
D10pep6a :	Ac - KK G A C S R S Q P E W E W L C A A - CONH2
D10pep7a:	Ac - KK G A C L L R A P E W G W L C A A - CONH2
D10pep10:	Ac - KK G A C M R G E W E W S W L C A A - CONH2
D10pep12:	Ac - K K G A C P P L N K E W A W L C A A - CONH2
Consensus Sequence	C X X X X X E W X W L C

Where:
G = glycine
A = alanine
C = cysteine
D = aspartic acid
L = leucine
K = lysine
E = glutamic acid
W = tryptophan
F = phenylalanine
R = arginine
H = histidine
S = serine
Q = glutamine

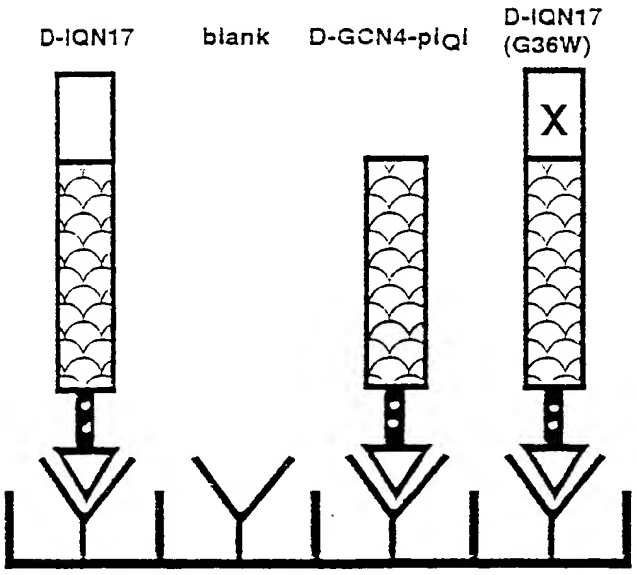
Figure 4.

1. Perform rounds of phage selection to identify binders to D-IQN17.



2. Sequence individual phage clones

3. Test for specificity of binding. Determine if the phage bind to the gp41 region of D-IQN17.



4. Synthesize D-peptides.

5. Assay anti-HIV activity of D-peptides.

Relationship of D-peptides to IQN17

Figure 5A

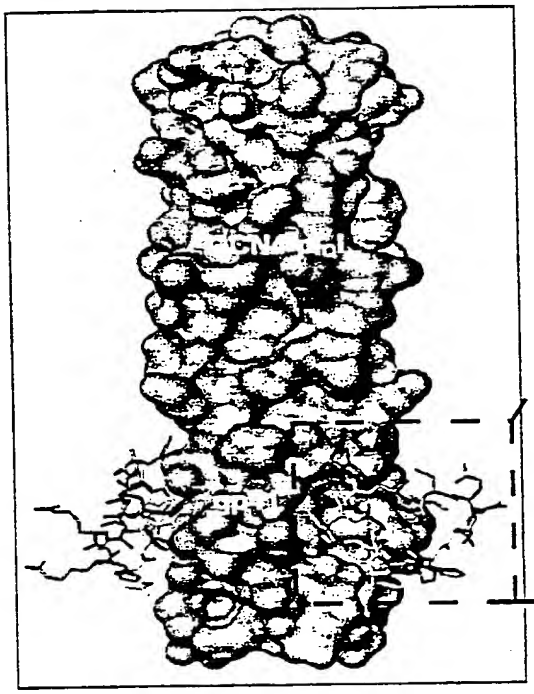


Figure 5B

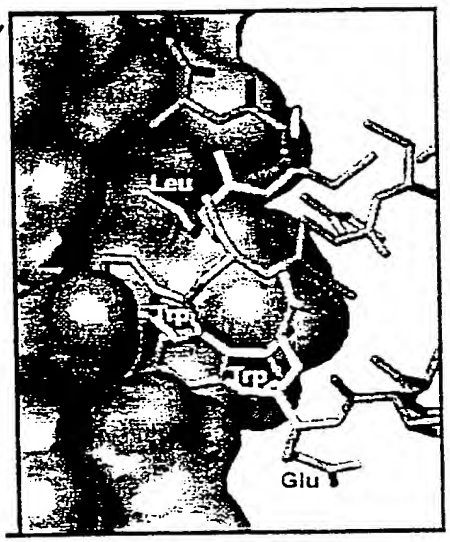


Figure 6A

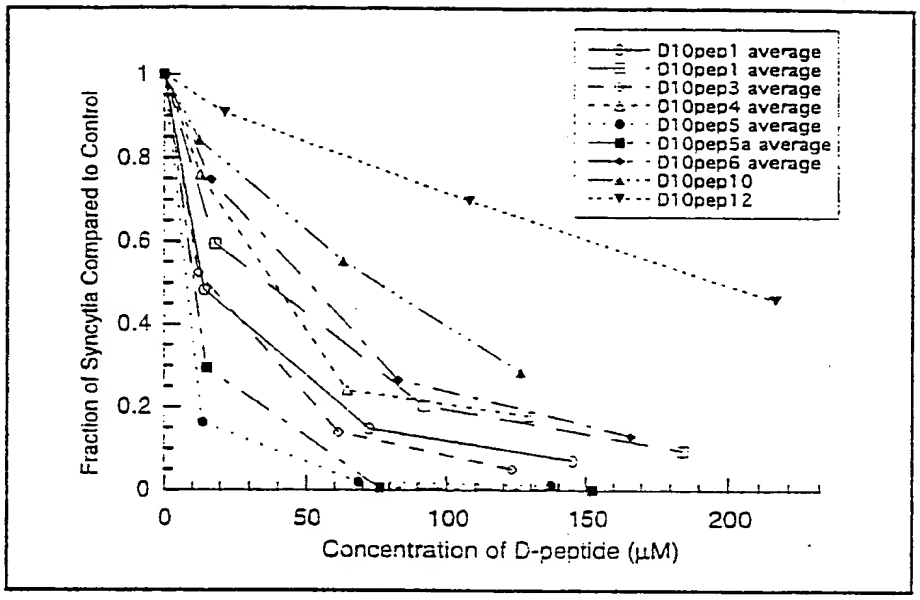


Figure 6B

D-Peptide	Approximate IC_{50} Value (from one or more experiments)
D10pep1	2×10^{-5} M
D10pep1A	3×10^{-5} M
D10pep3	1×10^{-5} M
D10pep4	3×10^{-5} M
D10pep5	3×10^{-6} M
D10pep5a	6×10^{-6} M
D10pep6	3×10^{-5} M
D10pep7a	4×10^{-5} M
Dpep10	6×10^{-5} M
Dpep12	2×10^{-4} M

D10pep3, D10pep4, D10pep5 } show anti-viral effects with IC_{50} values of less than 1×10^{-4} M.

```
REMARK   3
REMARK   3 REFINEMENT.
REMARK   3   PROGRAM     : CNS 0.5
REMARK   3   AUTHORS     : BRUNGER, ADAMS, CLORE, DELANO,
REMARK   3                 GROS, GROSSE-KUNSTLEVE, JIANG,
REMARK   3                 KUSZEWSKI, NILGES, PANNU, READ,
REMARK   3                 RICE, SIMONSON, WARREN
REMARK   3
REMARK   3  DATA USED IN REFINEMENT.
REMARK   3   RESOLUTION RANGE HIGH (ANGSTROMS) : 1.50
REMARK   3   RESOLUTION RANGE LOW  (ANGSTROMS) :10.00
REMARK   3   DATA CUTOFF            (SIGMA(F)) : 0.0
REMARK   3   DATA CUTOFF HIGH         (ABS(F)) :   646169.44
REMARK   3   DATA CUTOFF LOW          (ABS(F)) :     0.000000
REMARK   3   COMPLETENESS (WORKING+TEST)   (%) : 94.6
REMARK   3   NUMBER OF REFLECTIONS             : 13549
REMARK   3
REMARK   3  FIT TO DATA USED IN REFINEMENT.
REMARK   3   CROSS-VALIDATION METHOD           : THROUGHOUT
REMARK   3   FREE R VALUE TEST SET SELECTION   : RANDOM
REMARK   3   R VALUE            (WORKING SET) : 0.214
REMARK   3   FREE R VALUE                      : 0.245
REMARK   3   FREE R VALUE TEST SET SIZE   (%) : 10.1
REMARK   3   FREE R VALUE TEST SET COUNT       :  1362
REMARK   3   ESTIMATED ERROR OF FREE R VALUE   : 0.007
REMARK   3
REMARK   3  FIT IN THE HIGHEST RESOLUTION BIN.
REMARK   3   TOTAL NUMBER OF BINS USED           :   6
REMARK   3   BIN RESOLUTION RANGE HIGH       (A) : 1.50
REMARK   3   BIN RESOLUTION RANGE LOW        (A) : 1.59
REMARK   3   BIN COMPLETENESS (WORKING+TEST) (%) : 96.1
REMARK   3   REFLECTIONS IN BIN    (WORKING SET) :  2008
REMARK   3   BIN R VALUE           (WORKING SET) : 0.233
REMARK   3   BIN FREE R VALUE                    : 0.270
REMARK   3   BIN FREE R VALUE TEST SET SIZE  (%) :  9.8
REMARK   3   BIN FREE R VALUE TEST SET COUNT     :   219
REMARK   3   ESTIMATED ERROR OF BIN FREE R VALUE : 0.018
REMARK   3
REMARK   3  NUMBER OF NON-HYDROGEN ATOMS USED IN REFINEMENT.
REMARK   3   PROTEIN ATOMS            :    0
REMARK   3   NUCLEIC ACID ATOMS       :    0
REMARK   3   HETEROGEN ATOMS          :    0
REMARK   3   SOLVENT ATOMS            :    0
REMARK   3
REMARK   3  B VALUES.
REMARK   3   FROM WILSON PLOT           (A**2) : 21.6
REMARK   3   MEAN B VALUE      (OVERALL, A**2) : 29.7
REMARK   3   OVERALL ANISOTROPIC B VALUE.
REMARK   3    B11 (A**2) :  3.61
REMARK   3    B22 (A**2) :  3.61
REMARK   3    B33 (A**2) : -7.22
REMARK   3    B12 (A**2) :  1.74
REMARK   3    B13 (A**2) :  0.00
REMARK   3    B23 (A**2) :  0.00
REMARK   3
REMARK   3  BULK SOLVENT MODELING.
REMARK   3   METHOD USED : FLAT MODEL
REMARK   3   KSOL        : 0.394054
```

Figure 7A

```
REMARK   3   BSOL        : 58.3445 (A**2)
REMARK   3
REMARK   3  ESTIMATED COORDINATE ERROR.
REMARK   3   ESD FROM LUZZATI PLOT        (A) : 0.18
REMARK   3   ESD FROM SIGMAA              (A) : 0.09
REMARK   3   LOW RESOLUTION CUTOFF        (A) : 5.00
REMARK   3
REMARK   3  CROSS-VALIDATED ESTIMATED COORDINATE ERROR.
REMARK   3   ESD FROM C-V LUZZATI PLOT    (A) : 0.20
REMARK   3   ESD FROM C-V SIGMAA          (A) : 0.12
REMARK   3
REMARK   3  RMS DEVIATIONS FROM IDEAL VALUES.
REMARK   3   BOND LENGTHS                 (A) : 0.012
REMARK   3   BOND ANGLES            (DEGREES) : 1.5
REMARK   3   DIHEDRAL ANGLES        (DEGREES) : 15.7
REMARK   3   IMPROPER ANGLES        (DEGREES) : 1.00
REMARK   3
REMARK   3  ISOTROPIC THERMAL MODEL : RESTRAINED
REMARK   3
REMARK   3  ISOTROPIC THERMAL FACTOR RESTRAINTS.     RMS     SIGMA
REMARK   3   MAIN-CHAIN BOND              (A**2) : 0.956  ; 2.0
REMARK   3   MAIN-CHAIN ANGLE             (A**2) : 1.503  ; 3.0
REMARK   3   SIDE-CHAIN BOND              (A**2) : 1.853  ; 3.0
REMARK   3   SIDE-CHAIN ANGLE             (A**2) : 2.676  ; 3.5
REMARK   3
REMARK   3  NCS MODEL : NONE
REMARK   3
REMARK   3  NCS RESTRAINTS.                          RMS   SIGMA/WEIGHT
REMARK   3   GROUP  1  POSITIONAL              (A) : NULL  ; NULL
REMARK   3   GROUP  1  B-FACTOR           (A**2) : NULL  ; NULL
REMARK   3
REMARK   3  PARAMETER FILE  1  : protein_rep_d.param
REMARK   3  PARAMETER FILE  2  : CNS_TOPPAR/water_rep.param
REMARK   3  PARAMETER FILE  3  : CNS_TOPPAR/ion.param
REMARK   3  TOPOLOGY FILE  1   : CNS_TOPPAR/protein.top
REMARK   3  TOPOLOGY FILE  2   : CNS_TOPPAR/water.top
REMARK   3  TOPOLOGY FILE  3   : CNS_TOPPAR/ion.top
REMARK   3
REMARK   3  OTHER REFINEMENT REMARKS: NULL
SEQRES   1 A  214  ACE ARG MET LYS GLN ILE GLU ASP LYS ILE GLU GLU ILE
SEQRES   2 A  214  GLU SER LYS GLN LYS LYS ILE GLU ASN GLU ILE ALA ARG
SEQRES   3 A  214  ILE LYS LYS LEU LEU GLN LEU THR VAL TRP GLY ILE LYS
SEQRES   4 A  214  GLN LEU GLN ALA ARG ILE LEU ACE DLY DLA DCS DLU DLA
SEQRES   5 A  214  DRG DIS DRG DLU DRP DLA DRP DEU DCS DLA DLA CL WAT
SEQRES   6 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES   7 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES   8 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES   9 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  10 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  11 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  12 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  13 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  14 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  15 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  16 A  214  WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT WAT
SEQRES  17 A  214  WAT WAT WAT WAT WAT WAT
CRYST1   41.829   41.829   84.817  90.00  90.00 120.00 P 3 2 1          6
ORIGX1      1.000000  0.000000  0.000000        0.00000
```

Figure 7B

```
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.023907  0.013803  0.000000        0.00000
SCALE2      0.000000  0.027605  0.000000        0.00000
SCALE3      0.000000  0.000000  0.011790        0.00000
ATOM      1  CA  ACE A   0      26.830   7.813 -22.928  1.00 54.89      A
ATOM      2  C   ACE A   0      26.773   9.004 -22.017  1.00 54.85      A
ATOM      3  O   ACE A   0      25.855   9.820 -22.124  1.00 54.90      A
ATOM      4  N   ARG A   1      27.749   9.121 -21.217  1.00 54.75      A
ATOM      5  CA  ARG A   1      27.815  10.229 -20.165  1.00 54.58      A
ATOM      6  CB  ARG A   1      27.625  11.568 -20.887  1.00 54.54      A
ATOM      7  CG  ARG A   1      27.841  12.790 -20.010  1.00 54.10      A
ATOM      8  CD  ARG A   1      27.657  14.085 -20.800  1.00 54.18      A
ATOM      9  NE  ARG A   1      28.177  15.253 -20.086  1.00 54.02      A
ATOM     10  CZ  ARG A   1      29.470  15.495 -19.870  1.00 54.03      A
ATOM     11  NH1 ARG A   1      30.395  14.654 -20.312  1.00 53.79      A
ATOM     12  NH2 ARG A   1      29.843  16.587 -19.206  1.00 53.77      A
ATOM     13  C   ARG A   1      26.752  10.087 -19.074  1.00 54.54      A
ATOM     14  O   ARG A   1      27.042  10.224 -17.884  1.00 54.51      A
ATOM     15  N   MET A   2      25.518   9.809 -19.480  1.00 54.42      A
ATOM     16  CA  MET A   2      24.445   9.671 -18.515  1.00 54.44      A
ATOM     17  CB  MET A   2      23.074   9.796 -19.202  1.00 54.68      A
ATOM     18  CG  MET A   2      22.749   8.736 -20.238  1.00 54.76      A
ATOM     19  SD  MET A   2      21.345   9.252 -21.275  1.00 55.63      A
ATOM     20  CE  MET A   2      22.189   9.658 -22.822  1.00 55.29      A
ATOM     21  C   MET A   2      24.557   8.360 -17.755  1.00 54.51      A
ATOM     22  O   MET A   2      24.073   8.249 -16.629  1.00 54.42      A
ATOM     23  N   LYS A   3      25.208   7.372 -18.362  1.00 54.34      A
ATOM     24  CA  LYS A   3      25.383   6.082 -17.702  1.00 54.29      A
ATOM     25  CB  LYS A   3      26.212   5.139 -18.581  1.00 54.05      A
ATOM     26  CG  LYS A   3      26.527   3.786 -17.956  1.00 54.04      A
ATOM     27  CD  LYS A   3      27.727   3.853 -17.018  1.00 54.12      A
ATOM     28  CE  LYS A   3      28.108   2.469 -16.513  1.00 54.37      A
ATOM     29  NZ  LYS A   3      29.332   2.493 -15.656  1.00 53.92      A
ATOM     30  C   LYS A   3      26.097   6.344 -16.384  1.00 54.33      A
ATOM     31  O   LYS A   3      25.779   5.740 -15.353  1.00 54.60      A
ATOM     32  N   GLN A   4      27.064   7.255 -16.426  1.00 53.94      A
ATOM     33  CA  GLN A   4      27.811   7.626 -15.236  1.00 53.69      A
ATOM     34  CB  GLN A   4      28.845   8.699 -15.580  1.00 54.21      A
ATOM     35  CG  GLN A   4      29.861   8.974 -14.477  1.00 55.15      A
ATOM     36  CD  GLN A   4      29.621  10.285 -13.732  1.00 55.56      A
ATOM     37  OE1 GLN A   4      29.532  11.354 -14.343  1.00 56.19      A
ATOM     38  NE2 GLN A   4      29.533  10.209 -12.403  1.00 55.66      A
ATOM     39  C   GLN A   4      26.828   8.182 -14.212  1.00 53.19      A
ATOM     40  O   GLN A   4      26.972   7.953 -13.008  1.00 53.10      A
ATOM     41  N   ILE A   5      25.832   8.918 -14.705  1.00 52.58      A
ATOM     42  CA  ILE A   5      24.817   9.523 -13.853  1.00 51.70      A
ATOM     43  CB  ILE A   5      23.826  10.380 -14.687  1.00 51.71      A
ATOM     44  CG2 ILE A   5      22.643  10.812 -13.831  1.00 51.41      A
ATOM     45  CG1 ILE A   5      24.547  11.611 -15.246  1.00 51.48      A
ATOM     46  CD1 ILE A   5      23.646  12.569 -16.017  1.00 51.33      A
ATOM     47  C   ILE A   5      24.051   8.467 -13.060  1.00 51.26      A
ATOM     48  O   ILE A   5      23.650   8.700 -11.920  1.00 51.09      A
ATOM     49  N   GLU A   6      23.864   7.300 -13.662  1.00 50.54      A
ATOM     50  CA  GLU A   6      23.146   6.214 -13.013  1.00 50.01      A
ATOM     51  CB  GLU A   6      22.789   5.148 -14.043  1.00 50.43      A
ATOM     52  CG  GLU A   6      22.141   5.721 -15.289  1.00 51.26      A
ATOM     53  CD  GLU A   6      22.045   4.703 -16.400  1.00 51.68      A
```

Figure 7C

ATOM	54	OE1	GLU	A	6	23.016	3.931	-16.557	1.00	52.29	A
ATOM	55	OE2	GLU	A	6	21.019	4.682	-17.116	1.00	52.25	A
ATOM	56	C	GLU	A	6	23.995	5.606	-11.904	1.00	49.32	A
ATOM	57	O	GLU	A	6	23.475	5.210	-10.859	1.00	49.24	A
ATOM	58	N	ASP	A	7	25.302	5.527	-12.128	1.00	48.32	A
ATOM	59	CA	ASP	A	7	26.178	4.970	-11.113	1.00	47.23	A
ATOM	60	CB	ASP	A	7	27.543	4.626	-11.703	1.00	47.92	A
ATOM	61	CG	ASP	A	7	27.450	3.585	-12.788	1.00	48.33	A
ATOM	62	OD1	ASP	A	7	26.526	2.741	-12.729	1.00	48.43	A
ATOM	63	OD2	ASP	A	7	28.310	3.606	-13.690	1.00	48.94	A
ATOM	64	C	ASP	A	7	26.344	5.920	-9.926	1.00	46.09	A
ATOM	65	O	ASP	A	7	26.283	5.481	-8.773	1.00	45.71	A
ATOM	66	N	LYS	A	8	26.551	7.209	-10.201	1.00	44.57	A
ATOM	67	CA	LYS	A	8	26.703	8.195	-9.129	1.00	43.01	A
ATOM	68	CB	LYS	A	8	26.959	9.598	-9.708	1.00	43.49	A
ATOM	69	CG	LYS	A	8	25.895	10.076	-10.695	1.00	44.78	A
ATOM	70	CD	LYS	A	8	26.423	11.125	-11.702	1.00	45.38	A
ATOM	71	CE	LYS	A	8	26.698	12.490	-11.068	1.00	45.64	A
ATOM	72	NZ	LYS	A	8	27.153	13.499	-12.069	1.00	45.55	A
ATOM	73	C	LYS	A	8	25.413	8.171	-8.318	1.00	41.20	A
ATOM	74	O	LYS	A	8	25.419	8.346	-7.098	1.00	40.61	A
ATOM	75	N	ILE	A	9	24.302	7.935	-9.002	1.00	39.40	A
ATOM	76	CA	ILE	A	9	23.015	7.859	-8.333	1.00	37.29	A
ATOM	77	CB	ILE	A	9	21.872	7.859	-9.358	1.00	37.14	A
ATOM	78	CG2	ILE	A	9	20.600	7.251	-8.759	1.00	37.06	A
ATOM	79	CG1	ILE	A	9	21.631	9.303	-9.812	1.00	36.95	A
ATOM	80	CD1	ILE	A	9	20.801	9.440	-11.066	1.00	36.89	A
ATOM	81	C	ILE	A	9	22.927	6.638	-7.418	1.00	36.07	A
ATOM	82	O	ILE	A	9	22.450	6.756	-6.292	1.00	34.70	A
ATOM	83	N	GLU	A	10	23.389	5.478	-7.887	1.00	34.23	A
ATOM	84	CA	GLU	A	10	23.353	4.260	-7.074	1.00	33.04	A
ATOM	85	CB	GLU	A	10	23.884	3.013	-7.847	1.00	32.87	A
ATOM	86	CG	GLU	A	10	23.890	1.705	-6.991	1.00	33.10	A
ATOM	87	CD	GLU	A	10	24.287	0.417	-7.747	1.00	33.56	A
ATOM	88	OE1	GLU	A	10	24.327	0.442	-8.999	1.00	34.07	A
ATOM	89	OE2	GLU	A	10	24.542	-0.630	-7.084	1.00	32.41	A
ATOM	90	C	GLU	A	10	24.244	4.556	-5.878	1.00	32.53	A
ATOM	91	O	GLU	A	10	24.009	4.069	-4.779	1.00	32.14	A
ATOM	92	N	GLU	A	11	25.259	5.380	-6.100	1.00	31.82	A
ATOM	93	CA	GLU	A	11	26.165	5.731	-5.018	1.00	31.36	A
ATOM	94	CB	GLU	A	11	27.409	6.445	-5.536	1.00	33.18	A
ATOM	95	CG	GLU	A	11	28.358	6.833	-4.423	1.00	35.22	A
ATOM	96	CD	GLU	A	11	29.105	5.643	-3.822	1.00	36.93	A
ATOM	97	OE1	GLU	A	11	28.488	4.580	-3.575	1.00	38.03	A
ATOM	98	OE2	GLU	A	11	30.322	5.774	-3.579	1.00	38.85	A
ATOM	99	C	GLU	A	11	25.456	6.621	-3.998	1.00	30.15	A
ATOM	100	O	GLU	A	11	25.556	6.377	-2.798	1.00	28.89	A
ATOM	101	N	ILE	A	12	24.737	7.640	-4.471	1.00	29.09	A
ATOM	102	CA	ILE	A	12	24.017	8.533	-3.550	1.00	28.34	A
ATOM	103	CB	ILE	A	12	23.301	9.675	-4.325	1.00	28.74	A
ATOM	104	CG2	ILE	A	12	22.206	10.281	-3.501	1.00	28.70	A
ATOM	105	CG1	ILE	A	12	24.327	10.743	-4.701	1.00	28.84	A
ATOM	106	CD1	ILE	A	12	23.922	11.603	-5.890	1.00	29.69	A
ATOM	107	C	ILE	A	12	22.985	7.725	-2.761	1.00	27.83	A
ATOM	108	O	ILE	A	12	22.802	7.948	-1.560	1.00	26.46	A
ATOM	109	N	GLU	A	13	22.312	6.790	-3.423	1.00	27.40	A
ATOM	110	CA	GLU	A	13	21.313	5.965	-2.762	1.00	26.92	A
ATOM	111	CB	GLU	A	13	20.579	5.087	-3.805	1.00	28.34	A

Figure 7D

ATOM	112	CG	GLU	A	13	19.760	5.937	-4.810	1.00	29.72	A
ATOM	113	CD	GLU	A	13	19.080	5.118	-5.900	1.00	31.77	A
ATOM	114	OE1	GLU	A	13	19.671	4.107	-6.331	1.00	33.64	A
ATOM	115	OE2	GLU	A	13	17.960	5.495	-6.327	1.00	32.24	A
ATOM	116	C	GLU	A	13	21.975	5.110	-1.678	1.00	26.36	A
ATOM	117	O	GLU	A	13	21.411	4.912	-0.597	1.00	25.75	A
ATOM	118	N	SER	A	14	23.179	4.629	-1.950	1.00	26.17	A
ATOM	119	CA	SER	A	14	23.899	3.792	-0.999	1.00	26.31	A
ATOM	120	CB	SER	A	14	25.184	3.324	-1.625	1.00	26.71	A
ATOM	121	OG	SER	A	14	25.954	2.470	-0.695	1.00	30.07	A
ATOM	122	C	SER	A	14	24.246	4.626	0.221	1.00	25.81	A
ATOM	123	O	SER	A	14	24.079	4.149	1.339	1.00	25.13	A
ATOM	124	N	LYS	A	15	24.753	5.840	0.009	1.00	24.70	A
ATOM	125	CA	LYS	A	15	25.091	6.713	1.151	1.00	25.41	A
ATOM	126	CB	LYS	A	15	25.805	7.971	0.672	1.00	26.20	A
ATOM	127	CG	LYS	A	15	27.256	7.762	0.285	1.00	29.07	A
ATOM	128	CD	LYS	A	15	27.875	9.077	-0.220	1.00	30.97	A
ATOM	129	CE	LYS	A	15	29.328	8.914	-0.603	1.00	32.08	A
ATOM	130	NZ	LYS	A	15	29.547	7.749	-1.502	1.00	34.63	A
ATOM	131	C	LYS	A	15	23.824	7.102	1.938	1.00	24.45	A
ATOM	132	O	LYS	A	15	23.862	7.279	3.171	1.00	24.50	A
ATOM	133	N	GLN	A	16	22.708	7.254	1.247	1.00	24.12	A
ATOM	134	CA	GLN	A	16	21.450	7.586	1.904	1.00	23.82	A
ATOM	135	CB	GLN	A	16	20.396	7.815	0.834	1.00	25.71	A
ATOM	136	CG	GLN	A	16	19.229	8.643	1.232	1.00	29.64	A
ATOM	137	CD	GLN	A	16	18.543	9.230	0.004	1.00	32.26	A
ATOM	138	OE1	GLN	A	16	18.015	8.498	-0.817	1.00	34.89	A
ATOM	139	NE2	GLN	A	16	18.569	10.556	-0.135	1.00	32.74	A
ATOM	140	C	GLN	A	16	21.027	6.447	2.838	1.00	23.67	A
ATOM	141	O	GLN	A	16	20.584	6.681	3.979	1.00	22.84	A
ATOM	142	N	LYS	A	17	21.160	5.214	2.365	1.00	22.83	A
ATOM	143	CA	LYS	A	17	20.798	4.057	3.179	1.00	22.59	A
ATOM	144	CB	LYS	A	17	20.939	2.756	2.357	1.00	22.86	A
ATOM	145	CG	LYS	A	17	20.340	1.539	3.055	1.00	26.69	A
ATOM	146	CD	LYS	A	17	18.837	1.579	2.932	1.00	29.27	A
ATOM	147	CE	LYS	A	17	18.177	0.837	4.051	1.00	31.75	A
ATOM	148	NZ	LYS	A	17	16.686	0.870	3.940	1.00	34.25	A
ATOM	149	C	LYS	A	17	21.718	4.015	4.406	1.00	22.31	A
ATOM	150	O	LYS	A	17	21.261	3.747	5.515	1.00	21.02	A
ATOM	151	N	LYS	A	18	23.001	4.306	4.223	1.00	21.81	A
ATOM	152	CA	LYS	A	18	23.909	4.302	5.374	1.00	21.74	A
ATOM	153	CB	LYS	A	18	25.348	4.540	4.964	1.00	24.04	A
ATOM	154	CG	LYS	A	18	26.029	3.321	4.401	1.00	27.30	A
ATOM	155	CD	LYS	A	18	27.381	3.712	3.863	1.00	29.23	A
ATOM	156	CE	LYS	A	18	27.972	2.592	3.025	1.00	30.50	A
ATOM	157	NZ	LYS	A	18	29.290	3.010	2.472	1.00	33.57	A
ATOM	158	C	LYS	A	18	23.500	5.376	6.378	1.00	20.62	A
ATOM	159	O	LYS	A	18	23.565	5.138	7.577	1.00	19.85	A
ATOM	160	N	ILE	A	19	23.062	6.531	5.887	1.00	19.99	A
ATOM	161	CA	ILE	A	19	22.655	7.636	6.762	1.00	19.98	A
ATOM	162	CB	ILE	A	19	22.406	8.926	5.914	1.00	20.09	A
ATOM	163	CG2	ILE	A	19	21.554	9.944	6.682	1.00	20.80	A
ATOM	164	CG1	ILE	A	19	23.756	9.499	5.464	1.00	21.49	A
ATOM	165	CD1	ILE	A	19	23.669	10.495	4.296	1.00	21.19	A
ATOM	166	C	ILE	A	19	21.400	7.221	7.517	1.00	20.44	A
ATOM	167	O	ILE	A	19	21.282	7.452	8.735	1.00	20.23	A
ATOM	168	N	GLU	A	20	20.459	6.569	6.836	1.00	20.24	A
ATOM	169	CA	GLU	A	20	19.230	6.149	7.503	1.00	20.43	A

Figure 7E

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ATOM    170  CB  GLU A  20      18.223   5.608   6.484  1.00 22.94      A
ATOM    171  CG  GLU A  20      17.766   6.671   5.499  1.00 25.51      A
ATOM    172  CD  GLU A  20      16.926   6.108   4.378  1.00 29.04      A
ATOM    173  OE1 GLU A  20      16.961   4.873   4.177  1.00 30.40      A
ATOM    174  OE2 GLU A  20      16.242   6.901   3.691  1.00 30.73      A
ATOM    175  C   GLU A  20      19.533   5.109   8.576  1.00 20.88      A
ATOM    176  O   GLU A  20      18.917   5.127   9.645  1.00 20.23      A
ATOM    177  N   ASN A  21      20.478   4.220   8.321  1.00 20.53      A
ATOM    178  CA  ASN A  21      20.820   3.218   9.328  1.00 21.87      A
ATOM    179  CB  ASN A  21      21.694   2.117   8.720  1.00 24.15      A
ATOM    180  CG  ASN A  21      20.875   1.155   7.872  1.00 25.28      A
ATOM    181  OD1 ASN A  21      19.676   0.980   8.099  1.00 28.26      A
ATOM    182  ND2 ASN A  21      21.505   0.549   6.870  1.00 26.78      A
ATOM    183  C   ASN A  21      21.500   3.854  10.527  1.00 21.75      A
ATOM    184  O   ASN A  21      21.269   3.444  11.674  1.00 21.80      A
ATOM    185  N   GLU A  22      22.335   4.853  10.274  1.00 20.99      A
ATOM    186  CA  GLU A  22      23.007   5.548  11.369  1.00 20.36      A
ATOM    187  CB  GLU A  22      24.059   6.516  10.825  1.00 22.89      A
ATOM    188  CG  GLU A  22      24.914   7.169  11.901  1.00 25.86      A
ATOM    189  CD  GLU A  22      25.515   6.170  12.882  1.00 27.97      A
ATOM    190  OE1 GLU A  22      26.121   5.158  12.444  1.00 30.05      A
ATOM    191  OE2 GLU A  22      25.376   6.411  14.118  1.00 31.29      A
ATOM    192  C   GLU A  22      21.952   6.294  12.187  1.00 19.79      A
ATOM    193  O   GLU A  22      21.988   6.264  13.445  1.00 18.87      A
ATOM    194  N   ILE A  23      21.003   6.951  11.518  1.00 18.92      A
ATOM    195  CA  ILE A  23      19.955   7.670  12.254  1.00 18.60      A
ATOM    196  CB  ILE A  23      19.012   8.388  11.244  1.00 18.79      A
ATOM    197  CG2 ILE A  23      17.672   8.764  11.880  1.00 20.11      A
ATOM    198  CG1 ILE A  23      19.739   9.598  10.701  1.00 20.45      A
ATOM    199  CD1 ILE A  23      19.060  10.223   9.539  1.00 22.51      A
ATOM    200  C   ILE A  23      19.163   6.687  13.118  1.00 19.09      A
ATOM    201  O   ILE A  23      18.807   7.006  14.260  1.00 18.74      A
ATOM    202  N   ALA A  24      18.903   5.479  12.617  1.00 18.44      A
ATOM    203  CA  ALA A  24      18.153   4.517  13.420  1.00 18.86      A
ATOM    204  CB  ALA A  24      17.824   3.257  12.573  1.00 19.39      A
ATOM    205  C   ALA A  24      18.947   4.136  14.665  1.00 18.66      A
ATOM    206  O   ALA A  24      18.343   3.966  15.757  1.00 19.32      A
ATOM    207  N   ARG A  25      20.272   4.028  14.548  1.00 18.57      A
ATOM    208  CA  ARG A  25      21.111   3.667  15.709  1.00 19.19      A
ATOM    209  CB  ARG A  25      22.552   3.343  15.287  1.00 20.85      A
ATOM    210  CG  ARG A  25      22.674   1.959  14.627  1.00 23.87      A
ATOM    211  CD  ARG A  25      24.108   1.536  14.429  1.00 25.32      A
ATOM    212  NE  ARG A  25      24.759   2.294  13.376  1.00 27.13      A
ATOM    213  CZ  ARG A  25      24.672   2.019  12.075  1.00 27.60      A
ATOM    214  NH1 ARG A  25      23.955   0.979  11.641  1.00 28.92      A
ATOM    215  NH2 ARG A  25      25.296   2.806  11.214  1.00 27.79      A
ATOM    216  C   ARG A  25      21.083   4.819  16.722  1.00 18.69      A
ATOM    217  O   ARG A  25      20.942   4.592  17.940  1.00 17.93      A
ATOM    218  N   ILE A  26      21.201   6.041  16.221  1.00 17.83      A
ATOM    219  CA  ILE A  26      21.184   7.222  17.080  1.00 16.94      A
ATOM    220  CB  ILE A  26      21.369   8.479  16.225  1.00 17.99      A
ATOM    221  CG2 ILE A  26      20.943   9.741  17.006  1.00 19.34      A
ATOM    222  CG1 ILE A  26      22.821   8.537  15.796  1.00 19.88      A
ATOM    223  CD1 ILE A  26      23.144   9.587  14.721  1.00 21.83      A
ATOM    224  C   ILE A  26      19.876   7.301  17.857  1.00 18.02      A
ATOM    225  O   ILE A  26      19.875   7.580  19.055  1.00 17.73      A
ATOM    226  N   LYS A  27      18.752   7.069  17.191  1.00 17.60      A
ATOM    227  CA  LYS A  27      17.450   7.137  17.853  1.00 17.90      A
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Figure 7F

ATOM	228	CB	LYS	A	27	16.330	6.994	16.805	1.00	19.01	A
ATOM	229	CG	LYS	A	27	16.266	8.210	15.876	1.00	22.27	A
ATOM	230	CD	LYS	A	27	15.275	7.984	14.711	1.00	24.03	A
ATOM	231	CE	LYS	A	27	13.860	7.664	15.161	1.00	24.41	A
ATOM	232	NZ	LYS	A	27	13.173	8.848	15.714	1.00	27.04	A
ATOM	233	C	LYS	A	27	17.326	6.097	18.969	1.00	18.17	A
ATOM	234	O	LYS	A	27	16.767	6.388	20.013	1.00	18.33	A
ATOM	235	N	LYS	A	28	17.871	4.896	18.775	1.00	17.00	A
ATOM	236	CA	LYS	A	28	17.788	3.867	19.790	1.00	17.21	A
ATOM	237	CB	LYS	A	28	18.244	2.503	19.223	1.00	18.92	A
ATOM	238	CG	LYS	A	28	17.288	1.982	18.164	1.00	24.56	A
ATOM	239	CD	LYS	A	28	17.833	0.732	17.464	1.00	26.88	A
ATOM	240	CE	LYS	A	28	16.950	0.371	16.260	1.00	28.84	A
ATOM	241	NZ	LYS	A	28	17.284	-0.938	15.592	1.00	31.36	A
ATOM	242	C	LYS	A	28	18.618	4.257	21.016	1.00	17.36	A
ATOM	243	O	LYS	A	28	18.169	4.066	22.165	1.00	17.54	A
ATOM	244	N	LEU	A	29	19.794	4.835	20.793	1.00	16.84	A
ATOM	245	CA	LEU	A	29	20.642	5.234	21.912	1.00	16.41	A
ATOM	246	CB	LEU	A	29	22.077	5.529	21.453	1.00	16.26	A
ATOM	247	CG	LEU	A	29	23.050	6.048	22.515	1.00	16.76	A
ATOM	248	CD1	LEU	A	29	23.062	5.096	23.701	1.00	16.47	A
ATOM	249	CD2	LEU	A	29	24.450	6.201	21.885	1.00	17.67	A
ATOM	250	C	LEU	A	29	20.023	6.429	22.606	1.00	16.92	A
ATOM	251	O	LEU	A	29	20.027	6.503	23.859	1.00	16.36	A
ATOM	252	N	LEU	A	30	19.447	7.343	21.820	1.00	15.57	A
ATOM	253	CA	LEU	A	30	18.818	8.519	22.424	1.00	15.77	A
ATOM	254	CB	LEU	A	30	18.401	9.501	21.298	1.00	15.65	A
ATOM	255	CG	LEU	A	30	17.717	10.780	21.696	1.00	17.55	A
ATOM	256	CD1	LEU	A	30	18.557	11.504	22.722	1.00	16.71	A
ATOM	257	CD2	LEU	A	30	17.552	11.602	20.399	1.00	18.10	A
ATOM	258	C	LEU	A	30	17.659	8.067	23.288	1.00	16.42	A
ATOM	259	O	LEU	A	30	17.466	8.604	24.399	1.00	17.55	A
ATOM	260	N	GLN	A	31	16.903	7.053	22.862	1.00	16.79	A
ATOM	261	CA	GLN	A	31	15.816	6.564	23.692	1.00	18.13	A
ATOM	262	CB	GLN	A	31	14.945	5.593	22.886	1.00	21.45	A
ATOM	263	CG	GLN	A	31	14.119	6.258	21.834	1.00	24.92	A
ATOM	264	CD	GLN	A	31	13.196	7.437	22.424	1.00	26.81	A
ATOM	265	OE1	GLN	A	31	12.913	8.459	21.786	1.00	28.75	A
ATOM	266	NE2	GLN	A	31	12.713	7.207	23.648	1.00	29.86	A
ATOM	267	C	GLN	A	31	16.319	5.958	25.008	1.00	17.24	A
ATOM	268	O	GLN	A	31	15.655	6.092	26.038	1.00	17.79	A
ATOM	269	N	LEU	A	32	17.494	5.307	24.987	1.00	15.77	A
ATOM	270	CA	LEU	A	32	18.070	4.755	26.209	1.00	14.63	A
ATOM	271	CB	LEU	A	32	19.314	3.932	25.911	1.00	16.13	A
ATOM	272	CG	LEU	A	32	19.015	2.574	25.276	1.00	18.58	A
ATOM	273	CD1	LEU	A	32	20.291	1.961	24.770	1.00	20.70	A
ATOM	274	CD2	LEU	A	32	18.337	1.698	26.315	1.00	22.17	A
ATOM	275	C	LEU	A	32	18.449	5.895	27.140	1.00	13.68	A
ATOM	276	O	LEU	A	32	18.258	5.774	28.357	1.00	13.31	A
ATOM	277	N	THR	A	33	18.980	6.991	26.600	1.00	13.42	A
ATOM	278	CA	THR	A	33	19.348	8.081	27.500	1.00	12.96	A
ATOM	279	CB	THR	A	33	20.236	9.134	26.820	1.00	13.48	A
ATOM	280	OG1	THR	A	33	19.530	9.745	25.733	1.00	15.60	A
ATOM	281	CG2	THR	A	33	21.567	8.508	26.358	1.00	15.01	A
ATOM	282	C	THR	A	33	18.124	8.742	28.117	1.00	13.65	A
ATOM	283	O	THR	A	33	18.159	9.169	29.285	1.00	12.67	A
ATOM	284	N	VAL	A	34	17.038	8.838	27.345	1.00	13.20	A
ATOM	285	CA	VAL	A	34	15.804	9.410	27.863	1.00	13.88	A

Figure 7G

ATOM	286	CB	VAL	A	34	14.708	9.498	26.773	1.00	14.31	A
ATOM	287	CG1	VAL	A	34	13.380	9.811	27.382	1.00	15.35	A
ATOM	288	CG2	VAL	A	34	15.096	10.517	25.710	1.00	15.04	A
ATOM	289	C	VAL	A	34	15.326	8.526	29.041	1.00	12.55	A
ATOM	290	O	VAL	A	34	14.997	9.016	30.131	1.00	13.43	A
ATOM	291	N	TRP	A	35	15.354	7.210	28.857	1.00	13.04	A
ATOM	292	CA	TRP	A	35	14.946	6.289	29.908	1.00	13.11	A
ATOM	293	CB	TRP	A	35	14.988	4.861	29.319	1.00	14.19	A
ATOM	294	CG	TRP	A	35	14.672	3.785	30.334	1.00	15.43	A
ATOM	295	CD2	TRP	A	35	15.610	3.101	31.191	1.00	15.26	A
ATOM	296	CE2	TRP	A	35	14.860	2.165	31.963	1.00	15.57	A
ATOM	297	CE3	TRP	A	35	16.990	3.196	31.393	1.00	15.49	A
ATOM	298	CD1	TRP	A	35	13.454	3.258	30.609	1.00	17.15	A
ATOM	299	NE1	TRP	A	35	13.553	2.281	31.572	1.00	17.80	A
ATOM	300	CZ2	TRP	A	35	15.459	1.324	32.905	1.00	15.31	A
ATOM	301	CZ3	TRP	A	35	17.600	2.355	32.349	1.00	16.17	A
ATOM	302	CH2	TRP	A	35	16.815	1.437	33.090	1.00	14.74	A
ATOM	303	C	TRP	A	35	15.869	6.429	31.141	1.00	13.13	A
ATOM	304	O	TRP	A	35	15.418	6.409	32.278	1.00	12.76	A
ATOM	305	N	GLY	A	36	17.176	6.556	30.893	1.00	12.50	A
ATOM	306	CA	GLY	A	36	18.118	6.668	31.998	1.00	12.50	A
ATOM	307	C	GLY	A	36	17.887	7.936	32.817	1.00	11.58	A
ATOM	308	O	GLY	A	36	17.917	7.875	34.042	1.00	11.70	A
ATOM	309	N	ILE	A	37	17.656	9.084	32.174	1.00	11.85	A
ATOM	310	CA	ILE	A	37	17.383	10.303	32.884	1.00	11.18	A
ATOM	311	CB	ILE	A	37	17.262	11.439	31.882	1.00	11.22	A
ATOM	312	CG2	ILE	A	37	16.680	12.660	32.600	1.00	13.25	A
ATOM	313	CG1	ILE	A	37	18.636	11.739	31.281	1.00	12.70	A
ATOM	314	CD1	ILE	A	37	18.571	12.560	29.955	1.00	13.00	A
ATOM	315	C	ILE	A	37	16.082	10.105	33.703	1.00	11.99	A
ATOM	316	O	ILE	A	37	16.026	10.526	34.860	1.00	12.24	A
ATOM	317	N	LYS	A	38	15.069	9.465	33.094	1.00	11.84	A
ATOM	318	CA	LYS	A	38	13.825	9.215	33.809	1.00	13.62	A
ATOM	319	CB	LYS	A	38	12.840	8.512	32.861	1.00	15.00	A
ATOM	320	CG	LYS	A	38	11.429	8.437	33.369	1.00	17.76	A
ATOM	321	CD	LYS	A	38	10.545	7.835	32.247	1.00	20.78	A
ATOM	322	CE	LYS	A	38	9.046	7.955	32.600	1.00	25.34	A
ATOM	323	NZ	LYS	A	38	8.721	7.069	33.722	1.00	29.03	A
ATOM	324	C	LYS	A	38	14.060	8.399	35.083	1.00	12.64	A
ATOM	325	O	LYS	A	38	13.490	8.724	36.163	1.00	12.58	A
ATOM	326	N	GLN	A	39	14.916	7.371	35.001	1.00	11.99	A
ATOM	327	CA	GLN	A	39	15.176	6.573	36.189	1.00	11.84	A
ATOM	328	CB	GLN	A	39	16.049	5.339	35.900	1.00	12.90	A
ATOM	329	CG	GLN	A	39	15.580	4.440	34.757	1.00	14.71	A
ATOM	330	CD	GLN	A	39	14.118	4.213	34.747	1.00	17.73	A
ATOM	331	OE1	GLN	A	39	13.596	3.581	35.669	1.00	22.45	A
ATOM	332	NE2	GLN	A	39	13.420	4.701	33.701	1.00	20.02	A
ATOM	333	C	GLN	A	39	15.907	7.372	37.259	1.00	12.24	A
ATOM	334	O	GLN	A	39	15.601	7.271	38.453	1.00	12.42	A
ATOM	335	N	LEU	A	40	16.883	8.195	36.854	1.00	10.89	A
ATOM	336	CA	LEU	A	40	17.632	8.980	37.853	1.00	11.44	A
ATOM	337	CB	LEU	A	40	18.860	9.648	37.198	1.00	12.26	A
ATOM	338	CG	LEU	A	40	19.827	8.591	36.635	1.00	12.85	A
ATOM	339	CD1	LEU	A	40	21.007	9.367	36.066	1.00	16.06	A
ATOM	340	CD2	LEU	A	40	20.293	7.526	37.650	1.00	17.91	A
ATOM	341	C	LEU	A	40	16.763	10.046	38.497	1.00	10.71	A
ATOM	342	O	LEU	A	40	16.848	10.258	39.701	1.00	11.30	A
ATOM	343	N	GLN	A	41	15.911	10.692	37.704	1.00	11.62	A

Figure 7H

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ATOM    344  CA  GLN A  41      15.038  11.695  38.322  1.00 11.12      A
ATOM    345  CB  GLN A  41      14.241  12.447  37.257  1.00 11.92      A
ATOM    346  CG  GLN A  41      13.250  13.381  37.845  1.00 11.53      A
ATOM    347  CD  GLN A  41      12.280  13.933  36.838  1.00 12.64      A
ATOM    348  OE1 GLN A  41      11.814  13.226  35.962  1.00 13.16      A
ATOM    349  NE2 GLN A  41      11.972  15.220  36.973  1.00 13.67      A
ATOM    350  C   GLN A  41      14.081  11.031  39.332  1.00 10.98      A
ATOM    351  O   GLN A  41      13.883  11.585  40.404  1.00 12.39      A
ATOM    352  N   ALA A  42      13.571   9.845  38.994  1.00 12.53      A
ATOM    353  CA  ALA A  42      12.642   9.185  39.928  1.00 12.08      A
ATOM    354  CB  ALA A  42      12.035   7.954  39.295  1.00 13.83      A
ATOM    355  C   ALA A  42      13.383   8.856  41.218  1.00 14.57      A
ATOM    356  O   ALA A  42      12.820   8.975  42.296  1.00 15.73      A
ATOM    357  N   ARG A  43      14.647   8.446  41.147  1.00 13.64      A
ATOM    358  CA  ARG A  43      15.412   8.150  42.327  1.00 16.22      A
ATOM    359  CB  ARG A  43      16.772   7.626  41.852  1.00 18.06      A
ATOM    360  CG  ARG A  43      17.706   7.309  42.895  1.00 22.64      A
ATOM    361  CD  ARG A  43      17.232   6.108  43.679  1.00 25.20      A
ATOM    362  NE  ARG A  43      18.302   5.922  44.577  1.00 27.65      A
ATOM    363  CZ  ARG A  43      18.943   4.798  44.758  1.00 20.75      A
ATOM    364  NH1 ARG A  43      18.607   3.666  44.107  1.00 24.75      A
ATOM    365  NH2 ARG A  43      19.983   4.899  45.516  1.00 23.93      A
ATOM    366  C   ARG A  43      15.606   9.411  43.196  1.00 15.07      A
ATOM    367  O   ARG A  43      15.441   9.372  44.435  1.00 17.46      A
ATOM    368  N   ILE A  44      15.930  10.529  42.553  1.00 14.44      A
ATOM    369  CA  ILE A  44      16.181  11.794  43.242  1.00 14.63      A
ATOM    370  CB  ILE A  44      16.801  12.854  42.280  1.00 15.70      A
ATOM    371  CG2 ILE A  44      16.817  14.226  42.941  1.00 16.89      A
ATOM    372  CG1 ILE A  44      18.236  12.422  41.940  1.00 16.08      A
ATOM    373  CD1 ILE A  44      18.765  13.127  40.739  1.00 19.48      A
ATOM    374  C   ILE A  44      14.906  12.326  43.887  1.00 16.35      A
ATOM    375  O   ILE A  44      14.984  12.862  44.991  1.00 19.28      A
ATOM    376  N   LEU A  45      13.747  12.150  43.258  1.00 15.72      A
ATOM    377  CA  LEU A  45      12.515  12.682  43.883  1.00 15.80      A
ATOM    378  CB  LEU A  45      11.505  13.032  42.801  1.00 15.66      A
ATOM    379  CG  LEU A  45      11.867  14.181  41.878  1.00 15.35      A
ATOM    380  CD1 LEU A  45      10.793  14.298  40.823  1.00 17.37      A
ATOM    381  CD2 LEU A  45      11.954  15.485  42.701  1.00 18.49      A
ATOM    382  C   LEU A  45      11.903  11.710  44.867  1.00 18.22      A
ATOM    383  O   LEU A  45      11.053  12.187  45.658  1.00 19.14      A
ATOM    384  NT  LEU A  45      12.258  10.488  44.884  1.00 20.39      A
ATOM    385  CA  ACE D   0      10.275  -0.794  28.942  1.00 41.14      B
ATOM    386  C   ACE D   0      11.674  -0.285  28.785  1.00 40.52      B
ATOM    387  O   ACE D   0      11.905   0.677  28.016  1.00 41.12      B
ATOM    388  N   DLY D   1      12.631  -0.899  29.487  1.00 39.74      B
ATOM    389  CA  DLY D   1      13.997  -0.423  29.356  1.00 37.31      B
ATOM    390  C   DLY D   1      15.200  -1.051  30.044  1.00 35.38      B
ATOM    391  O   DLY D   1      15.133  -2.044  30.785  1.00 35.49      B
ATOM    392  N   DLA D   2      16.332  -0.424  29.752  1.00 33.19      B
ATOM    393  CA  DLA D   2      17.639  -0.797  30.279  1.00 31.99      B
ATOM    394  CB  DLA D   2      18.688   0.196  29.762  1.00 31.34      B
ATOM    395  C   DLA D   2      18.026  -2.217  29.871  1.00 31.71      B
ATOM    396  O   DLA D   2      18.611  -2.982  30.647  1.00 31.67      B
ATOM    397  N   DCS D   3      17.699  -2.577  28.640  1.00 30.76      B
ATOM    398  CA  DCS D   3      18.061  -3.892  28.159  1.00 31.11      B
ATOM    399  C   DCS D   3      17.104  -4.987  28.619  1.00 31.69      B
ATOM    400  O   DCS D   3      17.531  -6.020  29.111  1.00 31.85      B
ATOM    401  CB  DCS D   3      18.128  -3.876  26.638  1.00 30.00      B
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Figure 7I

ATOM	402	SG	DCS	D	3	19.502	-2.991	25.840	1.00	30.98	E
ATOM	403	N	DLU	D	4	15.813	-4.736	28.474	1.00	31.68	B
ATOM	404	CA	DLU	D	4	14.782	-5.702	28.834	1.00	32.07	B
ATOM	405	CB	DLU	D	4	13.397	-5.090	28.574	1.00	33.43	B
ATOM	406	CG	DLU	D	4	13.060	-4.844	27.093	1.00	35.53	B
ATOM	407	CD	DLU	D	4	13.663	-3.568	26.500	1.00	36.29	B
ATOM	408	OE1	DLU	D	4	14.422	-2.859	27.182	1.00	37.11	B
ATOM	409	OE2	DLU	D	4	13.367	-3.264	25.323	1.00	37.45	B
ATOM	410	C	DLU	D	4	14.875	-6.180	30.276	1.00	31.86	B
ATOM	411	O	DLU	D	4	14.832	-7.381	30.553	1.00	32.10	B
ATOM	412	N	DLA	D	5	15.022	-5.237	31.196	1.00	30.98	B
ATOM	413	CA	DLA	D	5	15.098	-5.566	32.611	1.00	30.61	B
ATOM	414	CB	DLA	D	5	14.984	-4.296	33.406	1.00	30.83	B
ATOM	415	C	DLA	D	5	16.362	-6.340	33.008	1.00	30.19	B
ATOM	416	O	DLA	D	5	16.387	-7.044	34.027	1.00	30.60	B
ATOM	417	N	DRG	D	6	17.418	-6.202	32.216	1.00	29.09	B
ATOM	418	CA	DRG	D	6	18.673	-6.893	32.489	1.00	28.71	B
ATOM	419	CB	DRG	D	6	18.480	-8.408	32.369	1.00	31.46	B
ATOM	420	CG	DRG	D	6	18.169	-8.847	30.969	1.00	34.88	B
ATOM	421	CD	DRG	D	6	19.397	-8.762	30.070	1.00	37.42	B
ATOM	422	NE	DRG	D	6	19.715	-7.408	29.607	1.00	40.28	B
ATOM	423	CZ	DRG	D	6	20.121	-7.134	28.370	1.00	40.89	B
ATOM	424	NH1	DRG	D	6	20.248	-8.118	27.481	1.00	42.76	B
ATOM	425	NH2	DRG	D	6	20.409	-5.891	28.015	1.00	42.55	B
ATOM	426	C	DRG	D	6	19.313	-6.582	33.833	1.00	27.29	B
ATOM	427	O	DRG	D	6	19.994	-7.423	34.421	1.00	27.43	B
ATOM	428	N	DIS	D	7	19.100	-5.379	34.342	1.00	24.49	B
ATOM	429	CA	DIS	D	7	19.731	-5.018	35.624	1.00	22.04	B
ATOM	430	CB	DIS	D	7	18.970	-3.888	36.284	1.00	22.68	B
ATOM	431	CG	DIS	D	7	17.655	-4.321	36.854	1.00	22.88	B
ATOM	432	CD2	DIS	D	7	17.178	-5.567	37.104	1.00	24.08	B
ATOM	433	ND1	DIS	D	7	16.650	-3.445	37.187	1.00	25.78	B
ATOM	434	CE1	DIS	D	7	15.595	-4.134	37.608	1.00	26.45	B
ATOM	435	NE2	DIS	D	7	15.894	-5.419	37.562	1.00	25.11	B
ATOM	436	C	DIS	D	7	21.156	-4.636	35.329	1.00	21.84	B
ATOM	437	O	DIS	D	7	21.412	-3.743	34.536	1.00	20.32	B
ATOM	438	N	DRG	D	8	22.091	-5.298	36.003	1.00	20.33	B
ATOM	439	CA	DRG	D	8	23.494	-5.122	35.778	1.00	19.80	B
ATOM	440	CB	DRG	D	8	24.284	-5.994	36.755	1.00	20.87	B
ATOM	441	CG	DRG	D	8	24.175	-7.428	36.459	1.00	26.97	B
ATOM	442	CD	DRG	D	8	24.743	-8.207	37.631	1.00	29.07	B
ATOM	443	NE	DRG	D	8	24.581	-9.603	37.325	1.00	31.54	B
ATOM	444	CZ	DRG	D	8	25.258	-10.199	36.352	1.00	31.94	B
ATOM	445	NH1	DRG	D	8	26.139	-9.485	35.658	1.00	33.88	B
ATOM	446	NH2	DRG	D	8	24.987	-11.432	36.027	1.00	33.88	B
ATOM	447	C	DRG	D	8	23.985	-3.711	35.873	1.00	17.95	B
ATOM	448	O	DRG	D	8	24.856	-3.361	35.124	1.00	17.42	B
ATOM	449	N	DLU	D	9	23.407	-2.934	36.783	1.00	16.93	B
ATOM	450	CA	DLU	D	9	23.900	-1.578	36.951	1.00	15.49	B
ATOM	451	CB	DLU	D	9	23.358	-0.954	38.261	1.00	16.03	B
ATOM	452	CG	DLU	D	9	21.876	-0.652	38.323	1.00	16.75	B
ATOM	453	CD	DLU	D	9	20.996	-1.816	38.786	1.00	16.82	B
ATOM	454	OE1	DLU	D	9	21.407	-2.982	38.584	1.00	19.63	B
ATOM	455	OE2	DLU	D	9	19.933	-1.498	39.310	1.00	20.12	B
ATOM	456	C	DLU	D	9	23.601	-0.717	35.747	1.00	15.97	B
ATOM	457	O	DLU	D	9	24.142	0.383	35.655	1.00	15.24	B
ATOM	458	N	DRP	D	10	22.747	-1.186	34.844	1.00	15.66	B
ATOM	459	CA	DRP	D	10	22.462	-0.435	33.611	1.00	15.31	B

Figure 7J

ATOM	460	CB	DRP	D	10	20.960	-0.187	33.420	1.00	16.05	B
ATOM	461	CG	DRP	D	10	20.354	0.791	34.410	1.00	15.28	B
ATOM	462	CD2	DRP	D	10	20.504	2.200	34.384	1.00	15.28	B
ATOM	463	CE2	DRP	D	10	19.734	2.730	35.424	1.00	15.74	B
ATOM	464	CE3	DRP	D	10	21.237	3.075	33.563	1.00	15.47	B
ATOM	465	CD1	DRP	D	10	19.504	0.512	35.449	1.00	16.40	B
ATOM	466	NE1	DRP	D	10	19.122	1.676	36.073	1.00	17.22	B
ATOM	467	CZ2	DRP	D	10	19.650	4.107	35.666	1.00	15.81	B
ATOM	468	CZ3	DRP	D	10	21.174	4.444	33.805	1.00	14.93	B
ATOM	469	CH2	DRP	D	10	20.382	4.935	34.850	1.00	15.26	B
ATOM	470	C	DRP	D	10	23.000	-1.140	32.376	1.00	17.32	B
ATOM	471	O	DRP	D	10	22.790	-0.682	31.244	1.00	16.59	B
ATOM	472	N	DLA	D	11	23.744	-2.227	32.572	1.00	17.72	B
ATOM	473	CA	DLA	D	11	24.253	-2.940	31.407	1.00	18.88	B
ATOM	474	CB	DLA	D	11	25.034	-4.168	31.867	1.00	20.11	B
ATOM	475	C	DLA	D	11	25.126	-2.074	30.501	1.00	18.95	B
ATOM	476	O	DLA	D	11	25.078	-2.221	29.267	1.00	21.13	B
ATOM	477	N	DRP	D	12	25.884	-1.142	31.084	1.00	17.86	B
ATOM	478	CA	DRP	D	12	26.759	-0.275	30.317	1.00	17.72	B
ATOM	479	CB	DRP	D	12	27.586	0.645	31.239	1.00	18.43	B
ATOM	480	CG	DRP	D	12	26.725	1.588	32.059	1.00	16.68	B
ATOM	481	CD2	DRP	D	12	26.285	2.900	31.676	1.00	16.49	B
ATOM	482	CE2	DRP	D	12	25.459	3.371	32.706	1.00	15.68	B
ATOM	483	CE3	DRP	D	12	26.519	3.714	30.561	1.00	17.14	B
ATOM	484	CD1	DRP	D	12	26.177	1.335	33.256	1.00	15.60	B
ATOM	485	NE1	DRP	D	12	25.402	2.400	33.668	1.00	15.74	B
ATOM	486	CZ2	DRP	D	12	24.842	4.628	32.664	1.00	15.78	B
ATOM	487	CZ3	DRP	D	12	25.904	4.977	30.525	1.00	17.42	B
ATOM	488	CH2	DRP	D	12	25.090	5.406	31.550	1.00	16.81	B
ATOM	489	C	DRP	D	12	25.913	0.577	29.346	1.00	18.81	B
ATOM	490	O	DRP	D	12	26.347	0.870	28.231	1.00	20.05	B
ATOM	491	N	DEU	D	13	24.740	1.020	29.790	1.00	17.43	B
ATOM	492	CA	DEU	D	13	23.915	1.866	28.926	1.00	17.59	B
ATOM	493	CB	DEU	D	13	22.883	2.647	29.756	1.00	15.97	B
ATOM	494	CG	DEU	D	13	21.857	3.489	28.971	1.00	15.31	B
ATOM	495	CD1	DEU	D	13	22.559	4.585	28.204	1.00	16.99	B
ATOM	496	CD2	DEU	D	13	20.886	4.105	29.938	1.00	16.07	B
ATOM	497	C	DEU	D	13	23.265	1.011	27.847	1.00	19.32	B
ATOM	498	O	DEU	D	13	23.224	1.429	26.702	1.00	20.12	B
ATOM	499	N	DCS	D	14	22.775	-0.180	28.199	1.00	20.93	B
ATOM	500	CA	DCS	D	14	22.190	-1.046	27.196	1.00	22.79	B
ATOM	501	C	DCS	D	14	23.272	-1.329	26.124	1.00	22.54	B
ATOM	502	O	DCS	D	14	22.963	-1.318	24.916	1.00	23.67	B
ATOM	503	CB	DCS	D	14	21.675	-2.319	27.874	1.00	23.47	B
ATOM	504	SG	DCS	D	14	21.216	-3.669	26.732	1.00	27.91	B
ATOM	505	N	DLA	D	15	24.514	-1.568	26.533	1.00	22.47	B
ATOM	506	CA	DLA	D	15	25.627	-1.857	25.614	1.00	23.31	B
ATOM	507	CB	DLA	D	15	26.868	-2.302	26.401	1.00	24.09	B
ATOM	508	C	DLA	D	15	25.987	-0.672	24.717	1.00	24.16	B
ATOM	509	O	DLA	D	15	26.511	-0.844	23.614	1.00	25.93	B
ATOM	510	N	DLA	D	16	25.723	0.544	25.192	1.00	22.60	B
ATOM	511	CA	DLA	D	16	26.017	1.743	24.400	1.00	22.10	B
ATOM	512	CB	DLA	D	16	26.006	2.985	25.314	1.00	22.02	B
ATOM	513	C	DLA	D	16	24.995	1.932	23.278	1.00	21.95	B
ATOM	514	O	DLA	D	16	25.355	2.570	22.256	1.00	22.36	B
ATOM	515	NT	DLA	D	16	23.843	1.460	23.410	1.00	23.47	B
ATOM	516	CL-1	CL	I	1	20.914	10.075	1.999	1.00	45.04	I
ATOM	517	OH2	WAT	W	1	23.911	6.454	-21.684	1.00	53.50	W

Figure 7K

ATOM	518	OH2	WAT	W	2	30.822	2.444	-19.357	1.00	52.17	W
ATOM	519	OH2	WAT	W	3	30.369	13.971	-17.693	1.00	37.33	W
ATOM	520	OH2	WAT	W	4	27.699	12.875	-16.588	1.00	46.63	W
ATOM	521	OH2	WAT	W	5	23.417	1.727	-13.168	1.00	48.41	W
ATOM	522	OH2	WAT	W	6	24.012	1.401	-16.007	1.00	58.65	W
ATOM	523	OH2	WAT	W	7	16.572	3.069	-7.418	1.00	36.12	W
ATOM	524	OH2	WAT	W	8	32.381	11.028	-8.334	1.00	55.01	W
ATOM	525	OH2	WAT	W	9	33.753	7.275	-10.261	1.00	53.14	W
ATOM	526	OH2	WAT	W	10	20.318	-0.862	-12.067	1.00	28.89	W
ATOM	527	OH2	WAT	W	11	26.434	1.459	-10.129	1.00	43.04	W
ATOM	528	OH2	WAT	W	12	27.878	0.323	-12.146	1.00	55.95	W
ATOM	529	OH2	WAT	W	13	31.427	0.259	-10.741	1.00	52.47	W
ATOM	530	OH2	WAT	W	14	29.889	8.411	-6.889	1.00	56.49	W
ATOM	531	OH2	WAT	W	15	22.532	1.843	-4.021	1.00	32.19	W
ATOM	532	OH2	WAT	W	16	23.814	-0.534	-4.336	1.00	39.56	W
ATOM	533	OH2	WAT	W	17	19.996	1.598	-5.292	1.00	33.28	W
ATOM	534	OH2	WAT	W	18	25.262	-3.040	-8.386	1.00	28.37	W
ATOM	535	OH2	WAT	W	19	22.556	0.000	0.001	1.00	30.95	W
ATOM	536	OH2	WAT	W	20	24.369	-1.421	-1.823	1.00	29.32	W
ATOM	537	OH2	WAT	W	21	29.134	-0.583	-6.291	1.00	46.18	W
ATOM	538	OH2	WAT	W	22	27.394	2.286	-5.533	1.00	43.67	W
ATOM	539	OH2	WAT	W	23	26.774	0.049	-4.387	1.00	45.47	W
ATOM	540	OH2	WAT	W	24	30.008	5.236	1.507	1.00	52.80	W
ATOM	541	OH2	WAT	W	25	27.776	4.560	0.356	1.00	42.94	W
ATOM	542	OH2	WAT	W	26	32.018	6.237	0.261	1.00	53.15	W
ATOM	543	OH2	WAT	W	28	18.650	4.426	-0.423	1.00	34.71	W
ATOM	544	OH2	WAT	W	29	18.919	1.842	-1.284	1.00	42.23	W
ATOM	545	OH2	WAT	W	30	11.826	6.239	7.700	1.00	59.49	W
ATOM	546	OH2	WAT	W	31	13.683	5.469	2.919	1.00	52.76	W
ATOM	547	OH2	WAT	W	32	16.956	4.594	1.380	1.00	47.84	W
ATOM	548	OH2	WAT	W	33	17.260	2.099	7.679	1.00	46.32	W
ATOM	549	OH2	WAT	W	34	17.636	1.737	-4.073	1.00	51.94	W
ATOM	550	OH2	WAT	W	35	16.221	5.835	9.764	1.00	30.19	W
ATOM	551	OH2	WAT	W	36	26.030	8.926	8.979	1.00	51.32	W
ATOM	552	OH2	WAT	W	37	13.758	2.898	9.624	1.00	52.05	W
ATOM	553	OH2	WAT	W	38	14.899	5.914	11.925	1.00	35.86	W
ATOM	554	OH2	WAT	W	39	19.841	0.030	14.724	1.00	45.90	W
ATOM	555	OH2	WAT	W	40	13.772	2.335	12.179	1.00	50.60	W
ATOM	556	OH2	WAT	W	41	13.367	0.805	6.229	1.00	51.80	W
ATOM	557	OH2	WAT	W	42	15.587	3.501	15.845	1.00	30.05	W
ATOM	558	OH2	WAT	W	43	14.280	4.098	13.819	1.00	48.74	W
ATOM	559	OH2	WAT	W	44	14.273	3.983	18.042	1.00	32.62	W
ATOM	560	OH2	WAT	W	45	14.275	2.720	20.720	1.00	40.19	W
ATOM	561	OH2	WAT	W	46	21.969	2.228	18.885	1.00	22.32	W
ATOM	562	OH2	WAT	W	47	21.588	1.778	21.594	1.00	28.43	W
ATOM	563	OH2	WAT	W	48	11.908	3.300	22.023	1.00	50.50	W
ATOM	564	OH2	WAT	W	49	13.679	0.626	18.643	1.00	46.64	W
ATOM	565	OH2	WAT	W	50	16.369	2.196	22.597	1.00	30.08	W
ATOM	566	OH2	WAT	W	51	12.828	6.527	18.634	1.00	37.29	W
ATOM	567	OH2	WAT	W	52	24.603	2.631	19.581	1.00	25.55	W
ATOM	568	OH2	WAT	W	53	11.867	0.791	23.131	1.00	58.27	W
ATOM	569	OH2	WAT	W	54	24.646	5.366	17.812	1.00	50.24	W
ATOM	570	OH2	WAT	W	55	20.954	0.091	17.131	1.00	49.14	W
ATOM	571	OH2	WAT	W	56	19.747	-0.562	21.394	1.00	36.92	W
ATOM	572	OH2	WAT	W	57	14.819	8.442	19.922	1.00	33.61	W
ATOM	573	OH2	WAT	W	58	10.854	5.349	19.724	1.00	45.89	W
ATOM	574	OH2	WAT	W	59	10.710	9.378	19.376	1.00	37.52	W
ATOM	575	OH2	WAT	W	60	10.497	10.303	21.845	1.00	34.96	W

Figure 7L

```
ATOM    576  OH2 WAT W  61      12.866   5.691  26.354  1.00 28.86      W
ATOM    577  OH2 WAT W  62      10.758   7.878  25.495  1.00 42.32      W
ATOM    578  OH2 WAT W  63      11.782   6.555  28.773  1.00 29.65      W
ATOM    579  OH2 WAT W  64      10.296   8.472  27.988  1.00 37.31      W
ATOM    580  OH2 WAT W  65      13.316   2.342  26.849  1.00 43.22      W
ATOM    581  OH2 WAT W  66      29.863  -1.693  28.654  1.00 38.41      W
ATOM    582  OH2 WAT W  67      16.468  -1.186  26.444  1.00 32.71      W
ATOM    583  OH2 WAT W  68      20.934  12.065  25.212  1.00 18.68      W
ATOM    584  OH2 WAT W  69       7.101   5.989  26.485  1.00 48.02      W
ATOM    585  OH2 WAT W  70       7.226  10.744  27.574  1.00 33.30      W
ATOM    586  OH2 WAT W  71      16.382  -1.374  34.997  1.00 34.36      W
ATOM    587  OH2 WAT W  72      17.474  -0.717  38.167  1.00 28.82      W
ATOM    588  OH2 WAT W  73      17.984  -2.951  33.186  1.00 27.39      W
ATOM    589  OH2 WAT W  74      16.999   1.929  37.830  1.00 37.09      W
ATOM    590  OH2 WAT W  75      20.595   3.071  39.121  1.00 19.51      W
ATOM    591  OH2 WAT W  76      14.326   5.004  39.584  1.00 20.31      W
ATOM    592  OH2 WAT W  77      11.973   4.544  38.034  1.00 32.93      W
ATOM    593  OH2 WAT W  78      18.317   4.417  39.397  1.00 44.00      W
ATOM    594  OH2 WAT W  79      10.983  -2.804  30.948  1.00 52.39      W
ATOM    595  OH2 WAT W  80      11.064   0.945  32.640  1.00 30.78      W
ATOM    596  OH2 WAT W  81      12.861   0.902  39.566  1.00 51.74      W
ATOM    597  OH2 WAT W  82      14.353  -1.379  39.210  1.00 48.06      W
ATOM    598  OH2 WAT W  83      13.014  -3.417  36.263  1.00 46.54      W
ATOM    599  OH2 WAT W  84      11.101  -2.319  39.669  1.00 61.24      W
ATOM    600  OH2 WAT W  85      20.879  -3.825  31.838  1.00 26.25      W
ATOM    601  OH2 WAT W  86      24.470  -4.753  28.192  1.00 36.86      W
ATOM    602  OH2 WAT W  87      22.117  -5.700  29.831  1.00 38.03      W
ATOM    603  OH2 WAT W  88      19.685   0.721  41.041  1.00 28.21      W
ATOM    604  OH2 WAT W  89      20.274   5.127  40.337  1.00 32.29      W
ATOM    605  OH2 WAT W  90      10.072   4.538  29.943  1.00 33.10      W
ATOM    606  OH2 WAT W  91      10.573   4.216  33.496  1.00 33.22      W
ATOM    607  OH2 WAT W  92      10.336   5.922  36.364  1.00 48.48      W
ATOM    608  OH2 WAT W  93       9.113   5.209  40.332  1.00 51.71      W
ATOM    609  OH2 WAT W  94       9.980   8.713  42.573  1.00 24.98      W
ATOM    610  OH2 WAT W  95      17.708   6.542  -1.798  1.00 36.93      W
ATOM    611  OH2 WAT W  96      10.278  11.397  38.730  1.00 17.13      W
ATOM    612  OH2 WAT W  97      11.290  10.478  36.184  1.00 15.62      W
ATOM    613  OH2 WAT W  98       8.444  12.988  37.395  1.00 17.25      W
ATOM    614  OH2 WAT W  99       8.735   9.911  40.361  1.00 25.18      W
ATOM    615  OH2 WAT W 100       6.665  11.917  35.865  1.00 28.95      W
ATOM    616  OH2 WAT W 101       8.907   9.736  35.113  1.00 28.77      W
ATOM    617  OH2 WAT W 102      10.416   5.919  42.300  1.00 32.80      W
ATOM    618  OH2 WAT W 103       8.278   3.600  38.536  1.00 54.85      W
ATOM    619  OH2 WAT W 104      14.183   7.249  45.734  1.00 23.53      W
ATOM    620  OH2 WAT W 105      11.426   7.965  46.547  1.00 34.68      W
ATOM    621  OH2 WAT W 106      16.907   2.218  41.970  1.00 39.50      W
ATOM    622  OH2 WAT W 107      16.479  14.336  46.761  1.00 23.72      W
ATOM    623  OH2 WAT W 108       8.319  12.931  45.022  1.00 22.11      W
ATOM    624  OH2 WAT W 109       7.189  12.423  42.385  1.00 39.34      W
ATOM    625  OH2 WAT W 110       8.599   9.769  44.603  1.00 40.15      W
ATOM    626  OH2 WAT W 111      26.891  -1.858  33.829  1.00 23.69      W
ATOM    627  OH2 WAT W 112      28.775  -3.310  32.521  1.00 38.13      W
ATOM    628  OH2 WAT W 113      31.335   0.587  33.068  1.00 34.37      W
ATOM    629  OH2 WAT W 114      30.921  -0.919  36.513  1.00 44.24      W
ATOM    630  OH2 WAT W 115      30.098   2.733  29.619  1.00 39.50      W
ATOM    631  OH2 WAT W 116      33.465   2.665  34.521  1.00 52.27      W
ATOM    632  OH2 WAT W 117      25.612  14.159 -18.301  1.00 56.10      W
ATOM    633  OH2 WAT W 118      33.904   2.165 -15.960  1.00 57.70      W
```

Figure 7M

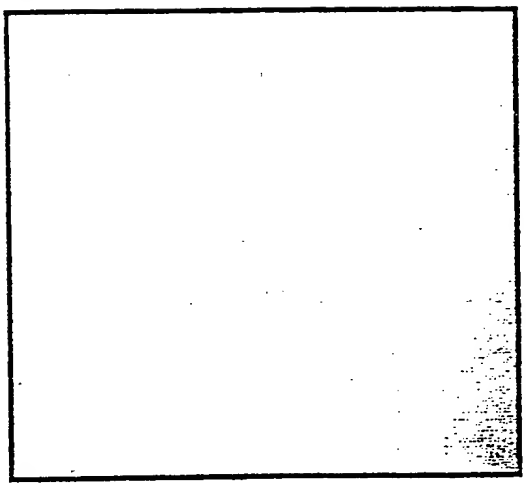
```
ATOM    634  OH2 WAT W 119      33.766   4.315 -14.106  1.00 57.44      W
ATOM    635  OH2 WAT W 120      26.831   7.497   7.075  1.00 40.38      W
ATOM    636  OH2 WAT W 121      26.562   8.206   4.240  1.00 32.00      W
ATOM    637  OH2 WAT W 122      29.081   7.039   3.251  1.00 46.30      W
ATOM    638  OH2 WAT W 123      22.080  -0.975  10.516  1.00 39.31      W
ATOM    639  OH2 WAT W 124      28.185   3.991  13.044  1.00 45.28      W
ATOM    640  OH2 WAT W 125      29.400   7.324  10.996  1.00 52.21      W
ATOM    641  OH2 WAT W 126      12.966   3.595  24.673  1.00 59.42      W
ATOM    642  OH2 WAT W 127       8.932   7.961  36.476  1.00 45.85      W
ATOM    643  OH2 WAT W 128      12.712   5.206  41.719  1.00 38.55      W
ATOM    644  OH2 WAT W 129       9.431  10.564  47.230  1.00 35.27      W
ATOM    645  OH2 WAT W 130       6.643   9.576  45.596  1.00 44.00      W
ATOM    646  OH2 WAT W 131      21.501  13.657  45.856  1.00 43.49      W
ATOM    647  OH2 WAT W 132      19.368  14.112  46.567  1.00 41.15      W
ATOM    648  OH2 WAT W 133      20.913  12.058  48.230  1.00 36.86      W
ATOM    649  OH2 WAT W 134      13.556   4.967  44.137  1.00 49.55      W
ATOM    650  OH2 WAT W 135      17.568   0.000   0.010  1.00 54.94      W
ATOM    651  OH2 WAT W 136      17.847  -0.139  11.093  1.00 42.03      W
ATOM    652  OH2 WAT W 137      25.734   4.074  15.641  1.00 35.36      W
ATOM    653  OH2 WAT W 138       8.107   7.930  38.831  1.00 37.47      W
ATOM    654  OH2 WAT W 139      10.614   4.603  44.378  1.00 61.10      W
ATOM    655  OH2 WAT W 140      14.180  -9.552  32.610  1.00 37.66      W
ATOM    656  OH2 WAT W 141      26.549  -4.072  22.858  1.00 48.05      W
ATOM    657  OH2 WAT W 142      21.688  -2.141  22.847  1.00 36.75      W
ATOM    658  OH2 WAT W 143      15.457   1.462  27.799  1.00 38.11      W
ATOM    659  OH2 WAT W 144      18.956  16.356  45.521  1.00 36.93      W
ATOM    660  OH2 WAT W 145      15.655   2.938  40.183  1.00 40.77      W
ATOM    661  OH2 WAT W 146      15.688  -1.613  19.777  1.00 47.04      W
ATOM    662  OH2 WAT W 147      26.880  -5.627  28.327  1.00 44.89      W
ATOM    663  OH2 WAT W 148      28.682  -5.605  33.707  1.00 43.34      W
ATOM    664  OH2 WAT W 149      28.220  11.179 -23.836  1.00 53.67      W
ATOM    665  OH2 WAT W 150      27.905   3.222  -7.774  1.00 44.54      W
ATOM    666  OH2 WAT W 151      15.403 -11.541  32.995  1.00 47.59      W
TER
END
```

Figure 7N

Figure 8A

Syncytia Assay with no D-peptide

Figure 8B



Syncytia Assay with [100 µM] peptide

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NMR Characterization of Aromatic Residues in IQN17/D-Peptide Complexes

Figure 9A

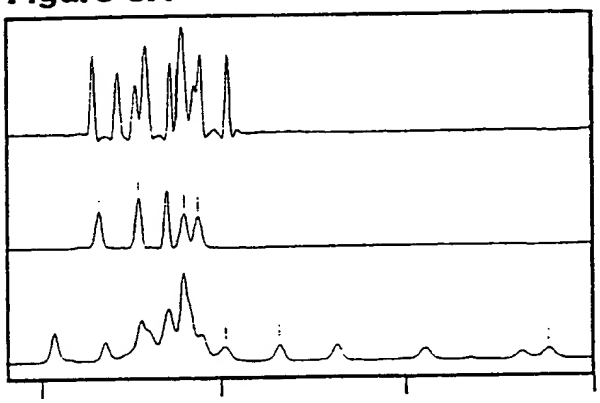


Figure 9B

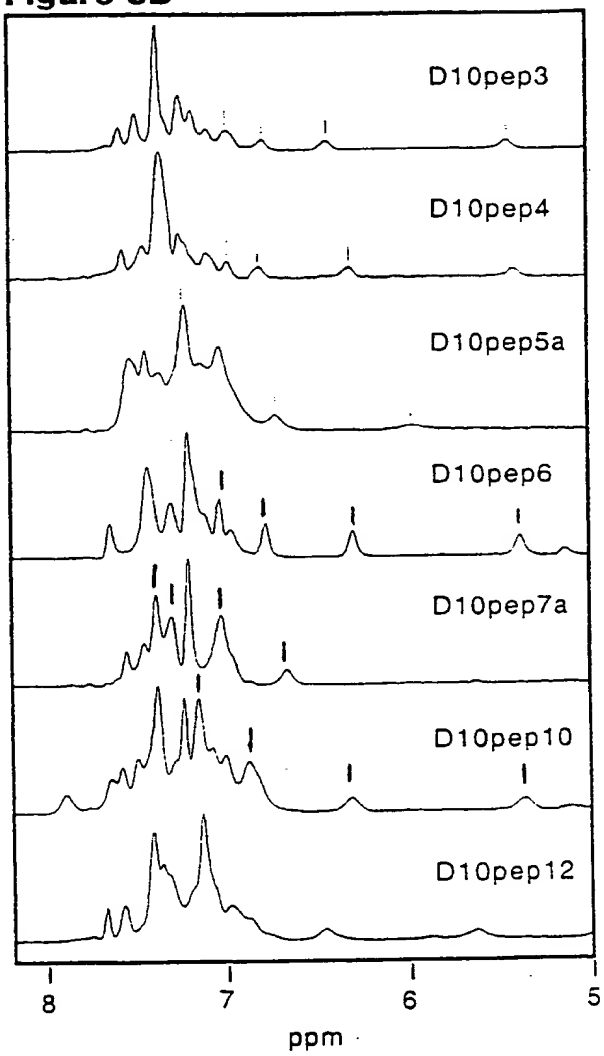


Figure 9C

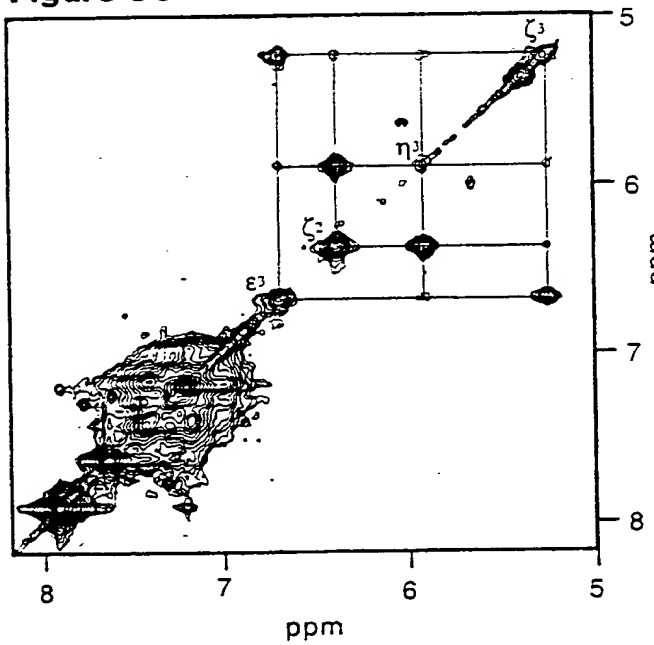
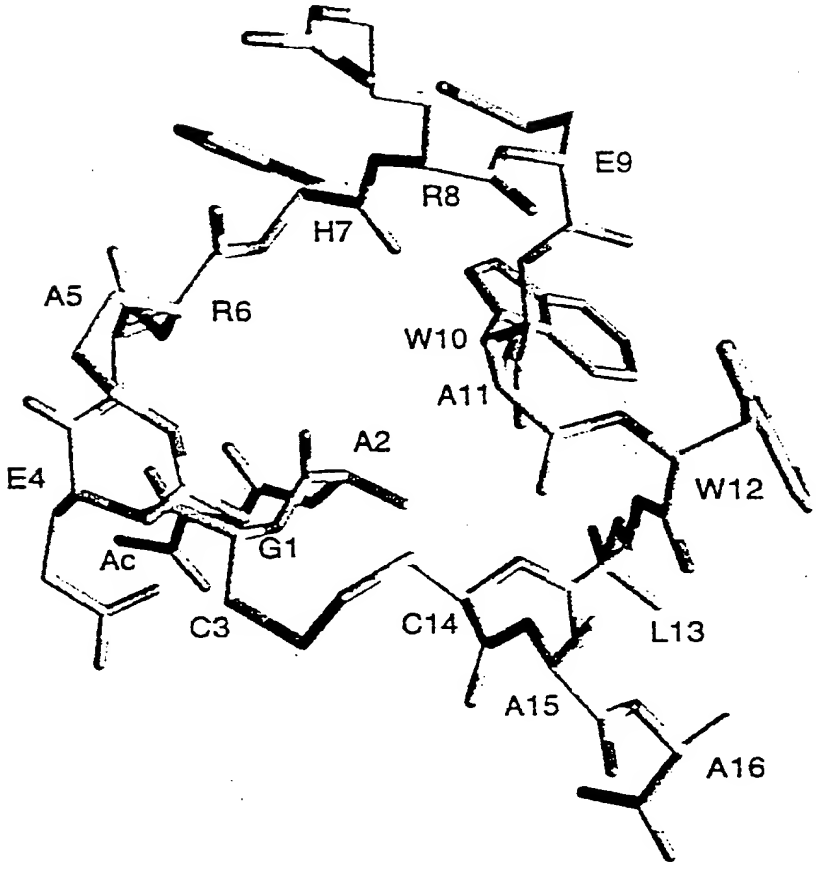


Figure 10: Conformation of D10pep1 in complex with IQN17



```
CRYST1   57.935  121.959   73.669  90.00  90.00  90.00 C2221           1
ORIGX1      1.000000  0.000000  0.000000        0.00000
ORIGX2      0.000000  1.000000  0.000000        0.00000
ORIGX3      0.000000  0.000000  1.000000        0.00000
SCALE1      0.017261  0.000000  0.000000        0.00000
SCALE2      0.000000  0.008199  0.000000        0.00000
SCALE3      0.000000  0.000000  0.013574        0.00000
ATOM      1  CA  ACE A   0      25.795  17.140  37.286  1.00 61.88      A
ATOM      2  C   ACE A   0      25.799  18.376  36.435  1.00 62.00      A
ATOM      3  O   ACE A   0      25.500  19.475  36.921  1.00 62.10      A
ATOM      4  N   ARG A   1      26.134  18.217  35.157  1.00 60.34      A
ATOM      5  CA  ARG A   1      26.203  19.328  34.217  1.00 60.56      A
ATOM      6  CB  ARG A   1      27.212  18.993  33.110  1.00 61.87      A
ATOM      7  CG  ARG A   1      27.630  20.135  32.212  1.00 60.78      A
ATOM      8  CD  ARG A   1      28.500  19.587  31.097  1.00 64.25      A
ATOM      9  NE  ARG A   1      29.018  20.628  30.217  1.00 65.07      A
ATOM     10  CZ  ARG A   1      29.706  20.377  29.109  1.00 63.90      A
ATOM     11  NH1 ARG A   1      29.951  19.124  28.766  1.00 64.20      A
ATOM     12  NH2 ARG A   1      30.157  21.367  28.351  1.00 63.51      A
ATOM     13  C   ARG A   1      24.823  19.573  33.595  1.00 59.45      A
ATOM     14  O   ARG A   1      24.453  20.714  33.294  1.00 57.69      A
ATOM     15  N   MET A   2      24.065  18.494  33.425  1.00 57.60      A
ATOM     16  CA  MET A   2      22.736  18.573  32.836  1.00 59.85      A
ATOM     17  CB  MET A   2      22.273  17.198  32.397  1.00 59.85      A
ATOM     18  CG  MET A   2      21.204  17.251  31.342  1.00 63.56      A
ATOM     19  SD  MET A   2      20.044  15.905  31.454  1.00 67.77      A
ATOM     20  CE  MET A   2      19.089  16.438  32.857  1.00 66.61      A
ATOM     21  C   MET A   2      21.723  19.130  33.834  1.00 61.33      A
ATOM     22  O   MET A   2      20.543  19.276  33.521  1.00 59.97      A
ATOM     23  N   LYS A   3      22.200  19.417  35.041  1.00 62.71      A
ATOM     24  CA  LYS A   3      21.373  19.961  36.107  1.00 63.07      A
ATOM     25  CB  LYS A   3      21.817  19.361  37.449  1.00 64.25      A
ATOM     26  CG  LYS A   3      20.982  19.721  38.687  1.00 64.89      A
ATOM     27  CD  LYS A   3      21.195  21.159  39.160  1.00 64.67      A
ATOM     28  CE  LYS A   3      20.543  21.405  40.525  1.00 64.66      A
ATOM     29  NZ  LYS A   3      19.077  21.123  40.548  1.00 63.04      A
ATOM     30  C   LYS A   3      21.599  21.467  36.062  1.00 64.55      A
ATOM     31  O   LYS A   3      20.639  22.245  36.032  1.00 64.65      A
ATOM     32  N   GLN A   4      22.869  21.873  36.036  1.00 64.34      A
ATOM     33  CA  GLN A   4      23.232  23.289  35.952  1.00 65.46      A
ATOM     34  CB  GLN A   4      24.746  23.447  35.780  1.00 67.71      A
ATOM     35  CG  GLN A   4      25.552  22.954  36.963  1.00 71.16      A
ATOM     36  CD  GLN A   4      25.297  23.771  38.212  1.00 75.18      A
ATOM     37  OE1 GLN A   4      25.618  24.962  38.269  1.00 77.70      A
ATOM     38  NE2 GLN A   4      24.706  23.135  39.225  1.00 76.77      A
ATOM     39  C   GLN A   4      22.508  23.928  34.758  1.00 64.11      A
ATOM     40  O   GLN A   4      22.191  25.128  34.776  1.00 62.08      A
ATOM     41  N   ILE A   5      22.260  23.120  33.726  1.00 59.80      A
ATOM     42  CA  ILE A   5      21.540  23.587  32.552  1.00 58.22      A
ATOM     43  CB  ILE A   5      21.567  22.558  31.398  1.00 56.85      A
ATOM     44  CG2 ILE A   5      20.438  22.851  30.416  1.00 53.92      A
ATOM     45  CG1 ILE A   5      22.942  22.562  30.719  1.00 56.47      A
ATOM     46  CD1 ILE A   5      23.079  21.524  29.614  1.00 59.50      A
ATOM     47  C   ILE A   5      20.083  23.928  32.929  1.00 58.98      A
ATOM     48  O   ILE A   5      19.575  24.928  32.729  1.00 58.48      A
ATOM     49  N   GLU A   6      19.424  22.796  33.472  1.00 59.29      A
ATOM     50  CA  GLU A   6      18.013  22.883  33.877  1.00 56.51      A
ATOM     51  CB  GLU A   6      17.528  21.537  34.448  1.00 55.59      A
```

Figure 11A

```
ATOM     52  CG  GLU A   6      17.638  20.359  33.480  1.00 56.46      A
ATOM     53  CD  GLU A   6      17.293  19.009  34.119  1.00 56.33      A
ATOM     54  OE1 GLU A   6      17.702  18.790  35.278  1.00 53.43      A
ATOM     55  OE2 GLU A   6      16.644  18.157  33.458  1.00 55.03      A
ATOM     56  C   GLU A   6      17.873  23.977  34.926  1.00 54.87      A
ATOM     57  O   GLU A   6      16.793  24.509  35.237  1.00 52.82      A
ATOM     58  N   ASP A   7      18.986  24.300  35.572  1.00 55.62      A
ATOM     59  CA  ASP A   7      19.039  25.336  36.597  1.00 56.65      A
ATOM     60  CB  ASP A   7      20.291  25.162  37.451  1.00 57.46      A
ATOM     61  CG  ASP A   7      20.010  24.471  38.762  1.00 57.37      A
ATOM     62  OD1 ASP A   7      19.180  23.534  38.775  1.00 53.78      A
ATOM     63  OD2 ASP A   7      20.637  24.862  39.771  1.00 57.66      A
ATOM     64  C   ASP A   7      19.034  26.745  36.041  1.00 56.99      A
ATOM     65  O   ASP A   7      18.516  27.662  36.678  1.00 55.43      A
ATOM     66  N   LYS A   8      19.632  26.945  34.873  1.00 58.30      A
ATOM     67  CA  LYS A   8      19.642  28.290  34.312  1.00 59.87      A
ATOM     68  CB  LYS A   8      20.971  28.599  33.612  1.00 62.61      A
ATOM     69  CG  LYS A   8      22.203  28.372  34.487  1.00 66.85      A
ATOM     70  CD  LYS A   8      23.232  29.498  34.357  1.00 70.21      A
ATOM     71  CE  LYS A   8      22.915  30.676  35.293  1.00 72.00      A
ATOM     72  NZ  LYS A   8      21.583  31.323  35.091  1.00 72.05      A
ATOM     73  C   LYS A   8      18.467  28.481  33.354  1.00 58.08      A
ATOM     74  O   LYS A   8      18.145  29.609  32.969  1.00 56.44      A
ATOM     75  N   ILE A   9      17.835  27.376  32.967  1.00 55.29      A
ATOM     76  CA  ILE A   9      16.668  27.436  32.099  1.00 56.69      A
ATOM     77  CB  ILE A   9      16.325  26.052  31.486  1.00 54.89      A
ATOM     78  CG2 ILE A   9      14.892  26.067  30.915  1.00 54.20      A
ATOM     79  CG1 ILE A   9      17.373  25.676  30.423  1.00 55.96      A
ATOM     80  CD1 ILE A   9      17.131  24.339  29.717  1.00 54.22      A
ATOM     81  C   ILE A   9      15.526  27.876  33.018  1.00 57.98      A
ATOM     82  O   ILE A   9      14.603  28.572  32.616  1.00 55.85      A
ATOM     83  N   GLU A  10      15.626  27.458  34.271  1.00 59.96      A
ATOM     84  CA  GLU A  10      14.641  27.788  35.283  1.00 61.12      A
ATOM     85  CB  GLU A  10      14.850  26.901  36.510  1.00 63.01      A
ATOM     86  CG  GLU A  10      13.846  27.117  37.618  1.00 66.89      A
ATOM     87  CD  GLU A  10      14.387  26.672  38.955  1.00 68.37      A
ATOM     88  OE1 GLU A  10      14.844  25.510  39.054  1.00 67.70      A
ATOM     89  OE2 GLU A  10      14.355  27.487  39.903  1.00 68.42      A
ATOM     90  C   GLU A  10      14.872  29.243  35.664  1.00 59.41      A
ATOM     91  O   GLU A  10      13.947  29.958  36.037  1.00 59.95      A
ATOM     92  N   GLU A  11      16.127  29.663  35.565  1.00 57.16      A
ATOM     93  CA  GLU A  11      16.524  31.024  35.893  1.00 55.88      A
ATOM     94  CB  GLU A  11      18.042  31.095  36.019  1.00 58.17      A
ATOM     95  CG  GLU A  11      18.569  32.375  36.627  1.00 62.73      A
ATOM     96  CD  GLU A  11      18.459  32.382  38.139  1.00 67.75      A
ATOM     97  OE1 GLU A  11      19.101  31.512  38.782  1.00 67.91      A
ATOM     98  OE2 GLU A  11      17.736  33.249  38.681  1.00 68.84      A
ATOM     99  C   GLU A  11      16.056  31.976  34.789  1.00 54.76      A
ATOM    100  O   GLU A  11      15.805  33.160  35.030  1.00 54.78      A
ATOM    101  N   ILE A  12      15.945  31.443  33.575  1.00 52.61      A
ATOM    102  CA  ILE A  12      15.510  32.210  32.414  1.00 50.09      A
ATOM    103  CB  ILE A  12      16.002  31.548  31.096  1.00 50.23      A
ATOM    104  CG2 ILE A  12      15.201  32.073  29.905  1.00 48.54      A
ATOM    105  CG1 ILE A  12      17.508  31.773  30.930  1.00 50.30      A
ATOM    106  CD1 ILE A  12      18.114  31.062  29.724  1.00 53.10      A
ATOM    107  C   ILE A  12      13.988  32.324  32.362  1.00 49.83      A
ATOM    108  O   ILE A  12      13.447  33.376  32.017  1.00 47.70      A
ATOM    109  N   GLU A  13      13.306  31.232  32.698  1.00 48.57      A
ATOM    110  CA  GLU A  13      11.849  31.219  32.677  1.00 48.32      A
ATOM    111  CB  GLU A  13      11.320  29.810  32.954  1.00 45.44      A
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Figure 11B

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ATOM    112  CG  GLU A  13      11.673  28.794  31.895  1.00 46.65      A
ATOM    113  CD  GLU A  13      11.419  27.372  32.358  1.00 49.90      A
ATOM    114  OE1 GLU A  13      12.051  26.968  33.366  1.00 49.96      A
ATOM    115  OE2 GLU A  13      10.599  26.665  31.720  1.00 50.18      A
ATOM    116  C   GLU A  13      11.357  32.163  33.749  1.00 47.83      A
ATOM    117  O   GLU A  13      10.279  32.731  33.638  1.00 48.72      A
ATOM    118  N   SER A  14      12.168  32.313  34.786  1.00 48.67      A
ATOM    119  CA  SER A  14      11.862  33.187  35.907  1.00 49.89      A
ATOM    120  CB  SER A  14      12.906  32.985  37.014  1.00 49.05      A
ATOM    121  OG  SER A  14      12.634  33.773  38.160  1.00 49.35      A
ATOM    122  C   SER A  14      11.885  34.627  35.415  1.00 50.52      A
ATOM    123  O   SER A  14      10.869  35.313  35.431  1.00 54.15      A
ATOM    124  N   LYS A  15      13.056  35.067  34.971  1.00 49.27      A
ATOM    125  CA  LYS A  15      13.248  36.416  34.474  1.00 51.02      A
ATOM    126  CB  LYS A  15      14.707  36.589  34.042  1.00 54.30      A
ATOM    127  CG  LYS A  15      15.018  37.931  33.417  1.00 58.79      A
ATOM    128  CD  LYS A  15      14.843  39.039  34.437  1.00 63.42      A
ATOM    129  CE  LYS A  15      15.841  38.880  35.576  1.00 65.66      A
ATOM    130  NZ  LYS A  15      15.722  39.983  36.569  1.00 68.14      A
ATOM    131  C   LYS A  15      12.313  36.758  33.305  1.00 50.99      A
ATOM    132  O   LYS A  15      12.022  37.926  33.061  1.00 49.62      A
ATOM    133  N   GLN A  16      11.848  35.740  32.587  1.00 50.06      A
ATOM    134  CA  GLN A  16      10.965  35.937  31.444  1.00 49.96      A
ATOM    135  CB  GLN A  16      10.950  34.684  30.570  1.00 49.89      A
ATOM    136  CG  GLN A  16      10.133  34.810  29.286  1.00 50.59      A
ATOM    137  CD  GLN A  16      10.287  33.603  28.369  1.00 54.27      A
ATOM    138  OE1 GLN A  16       9.799  32.511  28.667  1.00 56.28      A
ATOM    139  NE2 GLN A  16      10.985  33.796  27.250  1.00 54.69      A
ATOM    140  C   GLN A  16       9.551  36.256  31.899  1.00 50.61      A
ATOM    141  O   GLN A  16       8.788  36.931  31.195  1.00 48.56      A
ATOM    142  N   LYS A  17       9.198  35.736  33.067  1.00 49.38      A
ATOM    143  CA  LYS A  17       7.883  35.973  33.623  1.00 49.73      A
ATOM    144  CB  LYS A  17       7.582  34.982  34.750  1.00 52.97      A
ATOM    145  CG  LYS A  17       6.250  35.226  35.448  1.00 56.86      A
ATOM    146  CD  LYS A  17       6.066  34.276  36.618  1.00 59.31      A
ATOM    147  CE  LYS A  17       4.763  34.552  37.354  1.00 59.95      A
ATOM    148  NZ  LYS A  17       4.592  33.621  38.506  1.00 62.05      A
ATOM    149  C   LYS A  17       7.927  37.390  34.163  1.00 48.25      A
ATOM    150  O   LYS A  17       6.977  38.144  34.008  1.00 47.73      A
ATOM    151  N   LYS A  18       9.043  37.750  34.791  1.00 45.58      A
ATOM    152  CA  LYS A  18       9.190  39.101  35.309  1.00 45.26      A
ATOM    153  CB  LYS A  18      10.523  39.270  36.047  1.00 47.34      A
ATOM    154  CG  LYS A  18      10.627  38.493  37.362  1.00 50.10      A
ATOM    155  CD  LYS A  18      11.831  38.976  38.168  1.00 52.93      A
ATOM    156  CE  LYS A  18      11.869  38.358  39.550  1.00 55.07      A
ATOM    157  NZ  LYS A  18      12.933  38.968  40.398  1.00 59.20      A
ATOM    158  C   LYS A  18       9.107  40.110  34.171  1.00 41.59      A
ATOM    159  O   LYS A  18       8.585  41.206  34.349  1.00 42.70      A
ATOM    160  N   ILE A  19       9.633  39.740  33.008  1.00 40.25      A
ATOM    161  CA  ILE A  19       9.605  40.595  31.831  1.00 39.53      A
ATOM    162  CB  ILE A  19      10.494  40.015  30.710  1.00 42.08      A
ATOM    163  CG2 ILE A  19      10.133  40.631  29.369  1.00 41.71      A
ATOM    164  CG1 ILE A  19      11.969  40.214  31.074  1.00 42.52      A
ATOM    165  CD1 ILE A  19      12.939  39.656  30.039  1.00 43.29      A
ATOM    166  C   ILE A  19       8.172  40.725  31.325  1.00 39.27      A
ATOM    167  O   ILE A  19       7.751  41.790  30.899  1.00 37.81      A
ATOM    168  N   GLU A  20       7.421  39.637  31.372  1.00 39.00      A
ATOM    169  CA  GLU A  20       6.036  39.692  30.930  1.00 40.27      A
ATOM    170  CB  GLU A  20       5.437  38.280  30.834  1.00 43.21      A
ATOM    171  CG  GLU A  20       5.898  37.474  29.606  1.00 48.10      A
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Figure 11C

ATOM	172	CD	GLU	A	20	5.446	36.019	29.659	1.00	50.57	A
ATOM	173	OE1	GLU	A	20	5.832	35.316	30.617	1.00	52.42	A
ATOM	174	OE2	GLU	A	20	4.708	35.575	28.752	1.00	52.16	A
ATOM	175	C	GLU	A	20	5.195	40.546	31.873	1.00	40.09	A
ATOM	176	O	GLU	A	20	4.148	41.056	31.480	1.00	40.96	A
ATOM	177	N	ASN	A	21	5.637	40.694	33.119	1.00	38.83	A
ATOM	178	CA	ASN	A	21	4.880	41.498	34.071	1.00	40.69	A
ATOM	179	CB	ASN	A	21	5.216	41.107	35.507	1.00	39.42	A
ATOM	180	CG	ASN	A	21	4.618	39.768	35.892	1.00	41.35	A
ATOM	181	OD1	ASN	A	21	3.905	39.151	35.102	1.00	38.98	A
ATOM	182	ND2	ASN	A	21	4.902	39.312	37.107	1.00	40.82	A
ATOM	183	C	ASN	A	21	5.163	42.958	33.846	1.00	42.25	A
ATOM	184	O	ASN	A	21	4.261	43.801	33.872	1.00	42.61	A
ATOM	185	N	GLU	A	22	6.432	43.244	33.602	1.00	41.94	A
ATOM	186	CA	GLU	A	22	6.893	44.589	33.343	1.00	41.44	A
ATOM	187	CB	GLU	A	22	8.403	44.563	33.127	1.00	43.01	A
ATOM	188	CG	GLU	A	22	9.126	45.861	33.421	1.00	49.75	A
ATOM	189	CD	GLU	A	22	9.769	45.872	34.802	1.00	52.80	A
ATOM	190	OE1	GLU	A	22	10.611	44.988	35.077	1.00	53.66	A
ATOM	191	OE2	GLU	A	22	9.447	46.764	35.608	1.00	57.41	A
ATOM	192	C	GLU	A	22	6.188	45.082	32.068	1.00	41.34	A
ATOM	193	O	GLU	A	22	5.851	46.263	31.954	1.00	43.52	A
ATOM	194	N	ILE	A	23	5.964	44.175	31.116	1.00	37.55	A
ATOM	195	CA	ILE	A	23	5.295	44.530	29.863	1.00	35.10	A
ATOM	196	CB	ILE	A	23	5.418	43.408	28.800	1.00	36.19	A
ATOM	197	CG2	ILE	A	23	4.520	43.719	27.592	1.00	35.94	A
ATOM	198	CG1	ILE	A	23	6.876	43.288	28.340	1.00	39.18	A
ATOM	199	CD1	ILE	A	23	7.122	42.193	27.324	1.00	40.80	A
ATOM	200	C	ILE	A	23	3.816	44.827	30.093	1.00	33.36	A
ATOM	201	O	ILE	A	23	3.284	45.796	29.568	1.00	28.55	A
ATOM	202	N	ALA	A	24	3.167	43.981	30.881	1.00	30.41	A
ATOM	203	CA	ALA	A	24	1.760	44.147	31.179	1.00	30.11	A
ATOM	204	CB	ALA	A	24	1.276	42.994	32.043	1.00	27.29	A
ATOM	205	C	ALA	A	24	1.531	45.479	31.893	1.00	31.41	A
ATOM	206	O	ALA	A	24	0.562	46.183	31.608	1.00	31.49	A
ATOM	207	N	ARG	A	25	2.428	45.825	32.816	1.00	30.94	A
ATOM	208	CA	ARG	A	25	2.297	47.070	33.547	1.00	30.44	A
ATOM	209	CB	ARG	A	25	3.197	47.066	34.798	1.00	32.01	A
ATOM	210	CG	ARG	A	25	2.727	46.101	35.894	1.00	34.49	A
ATOM	211	CD	ARG	A	25	3.471	46.326	37.218	1.00	39.65	A
ATOM	212	NE	ARG	A	25	4.873	45.907	37.177	1.00	40.74	A
ATOM	213	CZ	ARG	A	25	5.308	44.687	37.496	1.00	43.06	A
ATOM	214	NH1	ARG	A	25	4.453	43.749	37.885	1.00	39.85	A
ATOM	215	NH2	ARG	A	25	6.606	44.399	37.399	1.00	40.30	A
ATOM	216	C	ARG	A	25	2.590	48.270	32.651	1.00	28.86	A
ATOM	217	O	ARG	A	25	1.907	49.296	32.728	1.00	29.35	A
ATOM	218	N	ILE	A	26	3.587	48.147	31.790	1.00	26.96	A
ATOM	219	CA	ILE	A	26	3.917	49.226	30.875	1.00	29.07	A
ATOM	220	CB	ILE	A	26	5.132	48.832	29.990	1.00	28.43	A
ATOM	221	CG2	ILE	A	26	5.239	49.760	28.799	1.00	25.38	A
ATOM	222	CG1	ILE	A	26	6.414	48.835	30.839	1.00	28.70	A
ATOM	223	CD1	ILE	A	26	7.646	48.257	30.132	1.00	27.77	A
ATOM	224	C	ILE	A	26	2.719	49.571	29.968	1.00	30.92	A
ATOM	225	O	ILE	A	26	2.435	50.746	29.690	1.00	32.33	A
ATOM	226	N	LYS	A	27	2.019	48.540	29.512	1.00	30.36	A
ATOM	227	CA	LYS	A	27	0.887	48.730	28.627	1.00	30.40	A
ATOM	228	CB	LYS	A	27	0.449	47.388	28.045	1.00	33.83	A
ATOM	229	CG	LYS	A	27	1.520	46.729	27.185	1.00	39.64	A
ATOM	230	CD	LYS	A	27	1.167	45.294	26.831	1.00	44.41	A
ATOM	231	CE	LYS	A	27	-0.086	45.204	26.003	1.00	46.84	A

Figure 11D

ATOM	232	NZ	LYS	A	27	-0.384	43.774	25.698	1.00	53.94	A
ATOM	233	C	LYS	A	27	-0.267	49.402	29.344	1.00	28.67	A
ATOM	234	O	LYS	A	27	-0.919	50.252	28.767	1.00	26.05	A
ATOM	235	N	LYS	A	28	-0.511	49.020	30.593	1.00	27.68	A
ATOM	236	CA	LYS	A	28	-1.597	49.609	31.371	1.00	27.30	A
ATOM	237	CB	LYS	A	28	-1.797	48.845	32.691	1.00	24.82	A
ATOM	238	CG	LYS	A	28	-2.961	49.384	33.573	1.00	27.48	A
ATOM	239	CD	LYS	A	28	-4.263	49.506	32.744	1.00	31.59	A
ATOM	240	CE	LYS	A	28	-5.526	49.699	33.606	1.00	30.02	A
ATOM	241	NZ	LYS	A	28	-5.440	50.820	34.586	1.00	31.11	A
ATOM	242	C	LYS	A	28	-1.284	51.076	31.641	1.00	29.57	A
ATOM	243	O	LYS	A	28	-2.164	51.951	31.566	1.00	28.21	A
ATOM	244	N	LEU	A	29	-0.017	51.359	31.923	1.00	29.36	A
ATOM	245	CA	LEU	A	29	0.385	52.723	32.179	1.00	33.70	A
ATOM	246	CB	LEU	A	29	1.822	52.745	32.692	1.00	35.26	A
ATOM	247	CG	LEU	A	29	2.023	53.727	33.847	1.00	38.04	A
ATOM	248	CD1	LEU	A	29	3.363	53.485	34.506	1.00	39.85	A
ATOM	249	CD2	LEU	A	29	1.891	55.149	33.332	1.00	38.01	A
ATOM	250	C	LEU	A	29	0.243	53.561	30.905	1.00	34.59	A
ATOM	251	O	LEU	A	29	-0.281	54.691	30.927	1.00	37.16	A
ATOM	252	N	LEU	A	30	0.721	53.020	29.792	1.00	34.03	A
ATOM	253	CA	LEU	A	30	0.616	53.724	28.528	1.00	35.56	A
ATOM	254	CB	LEU	A	30	1.230	52.874	27.414	1.00	38.09	A
ATOM	255	CG	LEU	A	30	1.470	53.508	26.050	1.00	40.19	A
ATOM	256	CD1	LEU	A	30	2.270	54.805	26.163	1.00	39.79	A
ATOM	257	CD2	LEU	A	30	2.215	52.484	25.198	1.00	45.44	A
ATOM	258	C	LEU	A	30	-0.882	53.980	28.263	1.00	34.76	A
ATOM	259	O	LEU	A	30	-1.269	55.050	27.794	1.00	33.56	A
ATOM	260	N	GLN	A	31	-1.713	52.996	28.572	1.00	30.55	A
ATOM	261	CA	GLN	A	31	-3.152	53.142	28.401	1.00	31.04	A
ATOM	262	CB	GLN	A	31	-3.865	51.839	28.782	1.00	33.01	A
ATOM	263	CG	GLN	A	31	-5.397	51.924	28.839	1.00	37.09	A
ATOM	264	CD	GLN	A	31	-6.045	50.582	29.159	1.00	45.53	A
ATOM	265	OE1	GLN	A	31	-5.715	49.940	30.159	1.00	52.72	A
ATOM	266	NE2	GLN	A	31	-6.973	50.151	28.310	1.00	46.91	A
ATOM	267	C	GLN	A	31	-3.633	54.303	29.273	1.00	31.34	A
ATOM	268	O	GLN	A	31	-4.419	55.125	28.832	1.00	28.45	A
ATOM	269	N	LEU	A	32	-3.141	54.376	30.509	1.00	30.93	A
ATOM	270	CA	LEU	A	32	-3.523	55.459	31.393	1.00	30.83	A
ATOM	271	CB	LEU	A	32	-2.988	55.237	32.811	1.00	29.49	A
ATOM	272	CG	LEU	A	32	-3.572	54.156	33.732	1.00	31.79	A
ATOM	273	CD1	LEU	A	32	-2.810	54.215	35.075	1.00	33.29	A
ATOM	274	CD2	LEU	A	32	-5.058	54.376	33.972	1.00	25.39	A
ATOM	275	C	LEU	A	32	-3.031	56.797	30.860	1.00	32.26	A
ATOM	276	O	LEU	A	32	-3.707	57.810	31.031	1.00	35.77	A
ATOM	277	N	THR	A	33	-1.872	56.798	30.198	1.00	31.70	A
ATOM	278	CA	THR	A	33	-1.298	58.019	29.640	1.00	33.33	A
ATOM	279	CB	THR	A	33	0.158	57.787	29.156	1.00	35.07	A
ATOM	280	OG1	THR	A	33	0.949	57.272	30.238	1.00	39.00	A
ATOM	281	CG2	THR	A	33	0.776	59.087	28.687	1.00	34.58	A
ATOM	282	C	THR	A	33	-2.120	58.560	28.471	1.00	33.63	A
ATOM	283	O	THR	A	33	-2.237	59.767	28.298	1.00	33.87	A
ATOM	284	N	VAL	A	34	-2.682	57.660	27.670	1.00	35.32	A
ATOM	285	CA	VAL	A	34	-3.507	58.046	26.531	1.00	36.90	A
ATOM	286	CB	VAL	A	34	-3.810	56.832	25.622	1.00	36.47	A
ATOM	287	CG1	VAL	A	34	-4.825	57.200	24.550	1.00	34.36	A
ATOM	288	CG2	VAL	A	34	-2.514	56.354	24.966	1.00	38.97	A
ATOM	289	C	VAL	A	34	-4.809	58.655	27.036	1.00	37.01	A
ATOM	290	O	VAL	A	34	-5.250	59.695	26.540	1.00	35.59	A
ATOM	291	N	TRP	A	35	-5.403	57.992	28.022	1.00	36.34	A

Figure 11E

ATOM	292	CA	TRP	A	35	-6.645	52.429	28.648	1.00	38.95	A
ATOM	293	CB	TRP	A	35	-7.022	57.429	29.743	1.00	44.03	A
ATOM	294	CG	TRP	A	35	-8.302	57.716	30.478	1.00	45.10	A
ATOM	295	CD2	TRP	A	35	-8.445	58.535	31.640	1.00	46.19	A
ATOM	296	CE2	TRP	A	35	-9.820	58.545	31.973	1.00	47.39	A
ATOM	297	CE3	TRP	A	35	-7.556	59.277	32.429	1.00	46.15	A
ATOM	298	CD1	TRP	A	35	-9.549	57.260	30.166	1.00	45.42	A
ATOM	299	NE1	TRP	A	35	-10.468	57.752	31.063	1.00	47.75	A
ATOM	300	CZ2	TRP	A	35	-10.317	59.258	33.067	1.00	48.12	A
ATOM	301	CZ3	TRP	A	35	-8.049	59.991	33.509	1.00	44.34	A
ATOM	302	CH2	TRP	A	35	-9.419	59.968	33.824	1.00	47.03	A
ATOM	303	C	TRP	A	35	-6.408	59.814	29.259	1.00	40.04	A
ATOM	304	O	TRP	A	35	-7.155	60.759	29.013	1.00	39.15	A
ATOM	305	N	GLY	A	36	-5.252	59.934	30.055	1.00	38.98	A
ATOM	306	CA	GLY	A	36	-5.039	61.211	30.658	1.00	38.44	A
ATOM	307	C	GLY	A	36	-5.034	62.327	29.634	1.00	38.41	A
ATOM	308	O	GLY	A	36	-5.626	63.390	29.845	1.00	40.58	A
ATOM	309	N	ILE	A	37	-4.356	62.094	28.517	1.00	39.01	A
ATOM	310	CA	ILE	A	37	-4.279	63.079	27.451	1.00	40.60	A
ATOM	311	CB	ILE	A	37	-3.395	62.584	26.301	1.00	40.20	A
ATOM	312	CG2	ILE	A	37	-3.509	63.517	25.136	1.00	39.97	A
ATOM	313	CG1	ILE	A	37	-1.939	62.477	26.767	1.00	41.25	A
ATOM	314	CD1	ILE	A	37	-1.036	61.777	25.778	1.00	38.31	A
ATOM	315	C	ILE	A	37	-5.662	63.366	26.886	1.00	42.00	A
ATOM	316	O	ILE	A	37	-6.019	64.516	26.654	1.00	42.52	A
ATOM	317	N	LYS	A	38	-6.438	62.317	26.660	1.00	42.56	A
ATOM	318	CA	LYS	A	38	-7.766	62.505	26.112	1.00	45.16	A
ATOM	319	CB	LYS	A	38	-8.459	61.156	25.925	1.00	46.50	A
ATOM	320	CG	LYS	A	38	-9.683	61.235	25.026	1.00	53.52	A
ATOM	321	CD	LYS	A	38	-10.840	62.017	25.651	1.00	55.55	A
ATOM	322	CE	LYS	A	38	-11.812	62.480	24.581	1.00	56.01	A
ATOM	323	NZ	LYS	A	38	-11.165	63.504	23.714	1.00	55.27	A
ATOM	324	C	LYS	A	38	-8.594	63.405	27.025	1.00	46.34	A
ATOM	325	O	LYS	A	38	-9.237	64.343	26.561	1.00	48.52	A
ATOM	326	N	GLN	A	39	-8.554	63.120	28.322	1.00	47.82	A
ATOM	327	CA	GLN	A	39	-9.303	63.877	29.318	1.00	49.21	A
ATOM	328	CB	GLN	A	39	-9.142	63.230	30.691	1.00	52.07	A
ATOM	329	CG	GLN	A	39	-9.431	61.742	30.727	1.00	59.01	A
ATOM	330	CD	GLN	A	39	-10.889	61.409	30.513	1.00	61.01	A
ATOM	331	OE1	GLN	A	39	-11.742	61.800	31.310	1.00	63.56	A
ATOM	332	NE2	GLN	A	39	-11.188	60.677	29.437	1.00	62.00	A
ATOM	333	C	GLN	A	39	-8.840	65.324	29.412	1.00	48.78	A
ATOM	334	O	GLN	A	39	-9.649	66.243	29.431	1.00	48.03	A
ATOM	335	N	LEU	A	40	-7.530	65.522	29.472	1.00	49.67	A
ATOM	336	CA	LEU	A	40	-6.980	66.861	29.590	1.00	50.78	A
ATOM	337	CB	LEU	A	40	-5.479	66.785	29.868	1.00	49.62	A
ATOM	338	CG	LEU	A	40	-4.736	68.118	29.982	1.00	47.99	A
ATOM	339	CD1	LEU	A	40	-5.416	69.030	31.011	1.00	51.32	A
ATOM	340	CD2	LEU	A	40	-3.300	67.852	30.376	1.00	48.82	A
ATOM	341	C	LEU	A	40	-7.227	67.736	28.363	1.00	53.20	A
ATOM	342	O	LEU	A	40	-7.230	68.964	28.457	1.00	53.67	A
ATOM	343	N	GLN	A	41	-7.433	67.104	27.215	1.00	56.61	A
ATOM	344	CA	GLN	A	41	-7.649	67.850	25.994	1.00	60.81	A
ATOM	345	CB	GLN	A	41	-7.295	66.994	24.781	1.00	60.00	A
ATOM	346	CG	GLN	A	41	-7.257	67.753	23.467	1.00	61.60	A
ATOM	347	CD	GLN	A	41	-6.756	66.885	22.330	1.00	61.14	A
ATOM	348	OE1	GLN	A	41	-5.630	66.377	22.367	1.00	56.12	A
ATOM	349	NE2	GLN	A	41	-7.598	66.697	21.316	1.00	60.61	A
ATOM	350	C	GLN	A	41	-9.084	68.344	25.915	1.00	63.54	A
ATOM	351	O	GLN	A	41	-9.388	69.277	25.179	1.00	65.13	A

Figure 11F

ATOM	352	N	ALA	A	42	-9.971	67.722	26.679	1.00	67.16	A
ATOM	353	CA	ALA	A	42	-11.362	68.150	26.693	1.00	70.08	A
ATOM	354	CB	ALA	A	42	-12.252	67.043	27.249	1.00	68.59	A
ATOM	355	C	ALA	A	42	-11.461	69.423	27.556	1.00	72.76	A
ATOM	356	O	ALA	A	42	-12.506	69.748	28.123	1.00	73.45	A
ATOM	357	N	ARG	A	43	-10.338	70.137	27.642	1.00	75.35	A
ATOM	358	CA	ARG	A	43	-10.202	71.377	28.413	1.00	76.97	A
ATOM	359	CB	ARG	A	43	-9.391	71.131	29.705	1.00	77.23	A
ATOM	360	CG	ARG	A	43	-10.130	70.250	30.753	1.00	77.83	A
ATOM	361	CD	ARG	A	43	-9.265	69.690	31.889	1.00	76.18	A
ATOM	362	NE	ARG	A	43	-10.053	68.919	32.864	1.00	76.19	A
ATOM	363	CZ	ARG	A	43	-10.933	67.967	32.551	1.00	76.17	A
ATOM	364	NH1	ARG	A	43	-11.153	67.657	31.284	1.00	76.24	A
ATOM	365	NH2	ARG	A	43	-11.605	67.326	33.507	1.00	77.89	A
ATOM	366	C	ARG	A	43	-9.560	72.481	27.570	1.00	79.19	A
ATOM	367	O	ARG	A	43	-10.131	72.882	26.548	1.00	79.42	A
ATOM	368	N	ILE	A	44	-8.381	72.970	27.993	1.00	81.42	A
ATOM	369	CA	ILE	A	44	-7.646	74.059	27.276	1.00	84.32	A
ATOM	370	CB	ILE	A	44	-6.073	73.998	27.495	1.00	84.97	A
ATOM	371	CG2	ILE	A	44	-5.292	74.824	26.419	1.00	85.80	A
ATOM	372	CG1	ILE	A	44	-5.728	74.612	28.829	1.00	85.52	A
ATOM	373	CD1	ILE	A	44	-6.344	76.011	29.055	1.00	87.04	A
ATOM	374	C	ILE	A	44	-7.908	73.987	25.790	1.00	86.80	A
ATOM	375	O	ILE	A	44	-8.577	74.829	25.234	1.00	87.60	A
ATOM	376	N	LEU	A	45	-7.318	73.007	25.145	1.00	87.99	A
ATOM	377	CA	LEU	A	45	-7.541	72.910	23.737	1.00	88.13	A
ATOM	378	CB	LEU	A	45	-6.257	72.509	23.009	1.00	88.79	A
ATOM	379	CG	LEU	A	45	-5.940	73.339	21.770	1.00	90.46	A
ATOM	380	CD1	LEU	A	45	-7.147	73.370	20.837	1.00	91.58	A
ATOM	381	CD2	LEU	A	45	-5.596	74.779	22.173	1.00	90.84	A
ATOM	382	C	LEU	A	45	-8.656	71.944	23.376	1.00	88.30	A
ATOM	383	O	LEU	A	45	-9.507	71.665	24.291	1.00	87.82	A
ATOM	384	NT	LEU	A	45	-8.614	71.561	22.151	1.00	88.77	A
ATOM	385	CA	ACE	B	0	29.175	18.175	21.874	1.00	35.90	B
ATOM	386	C	ACE	B	0	27.867	18.849	22.146	1.00	36.69	B
ATOM	387	O	ACE	B	0	27.836	20.078	22.299	1.00	33.24	B
ATOM	388	N	ARG	B	1	26.771	18.065	22.218	1.00	32.69	B
ATOM	389	CA	ARG	B	1	25.440	18.590	22.450	1.00	34.24	B
ATOM	390	CB	ARG	B	1	24.436	17.446	22.644	1.00	33.49	B
ATOM	391	CG	ARG	B	1	22.976	17.878	22.651	1.00	32.92	B
ATOM	392	CD	ARG	B	1	22.436	18.177	21.260	1.00	34.95	B
ATOM	393	NE	ARG	B	1	22.366	16.972	20.443	1.00	38.88	B
ATOM	394	CZ	ARG	B	1	21.548	15.952	20.706	1.00	42.79	B
ATOM	395	NH1	ARG	B	1	20.740	16.012	21.765	1.00	44.66	B
ATOM	396	NH2	ARG	B	1	21.550	14.868	19.943	1.00	39.72	B
ATOM	397	C	ARG	B	1	25.424	19.498	23.685	1.00	35.96	B
ATOM	398	O	ARG	B	1	24.920	20.617	23.628	1.00	36.55	B
ATOM	399	N	MET	B	2	26.008	19.009	24.779	1.00	39.89	B
ATOM	400	CA	MET	B	2	26.077	19.769	26.022	1.00	43.08	B
ATOM	401	CB	MET	B	2	27.113	19.163	26.972	1.00	43.87	B
ATOM	402	CG	MET	B	2	26.728	17.847	27.623	1.00	46.86	B
ATOM	403	SD	MET	B	2	25.304	18.010	28.700	1.00	52.01	B
ATOM	404	CE	MET	B	2	24.024	18.375	27.524	1.00	52.70	B
ATOM	405	C	MET	B	2	26.440	21.219	25.789	1.00	45.76	B
ATOM	406	O	MET	B	2	25.723	22.121	26.212	1.00	44.09	B
ATOM	407	N	LYS	B	3	27.570	21.414	25.125	1.00	47.94	B
ATOM	408	CA	LYS	B	3	28.082	22.736	24.820	1.00	52.42	B
ATOM	409	CB	LYS	B	3	29.455	22.565	24.151	1.00	54.64	B
ATOM	410	CG	LYS	B	3	30.552	23.540	24.595	1.00	58.36	B
ATOM	411	CD	LYS	B	3	30.382	24.937	24.030	1.00	60.17	B

Figure 11G

ATOM	412	CE	LYS	B	3	31.618	25.777	24.321	1.00	62.06	B
ATOM	413	NZ	LYS	B	3	31.561	27.140	23.704	1.00	63.71	B
ATOM	414	C	LYS	B	3	27.095	23.479	23.907	1.00	52.65	B
ATOM	415	O	LYS	B	3	26.858	24.671	24.092	1.00	52.44	B
ATOM	416	N	GLN	B	4	26.517	22.774	22.934	1.00	52.13	B
ATOM	417	CA	GLN	B	4	25.549	23.387	22.032	1.00	54.04	B
ATOM	418	CB	GLN	B	4	24.930	22.330	21.105	1.00	57.72	B
ATOM	419	CG	GLN	B	4	25.792	21.880	19.925	1.00	60.44	B
ATOM	420	CD	GLN	B	4	25.855	22.923	18.816	1.00	62.71	B
ATOM	421	OE1	GLN	B	4	26.404	24.017	18.997	1.00	64.51	B
ATOM	422	NE2	GLN	B	4	25.276	22.592	17.661	1.00	62.62	B
ATOM	423	C	GLN	B	4	24.441	24.062	22.836	1.00	52.63	B
ATOM	424	O	GLN	B	4	24.013	25.162	22.518	1.00	53.56	B
ATOM	425	N	ILE	B	5	23.982	23.379	23.878	1.00	52.62	B
ATOM	426	CA	ILE	B	5	22.929	23.880	24.758	1.00	52.43	B
ATOM	427	CB	ILE	B	5	22.443	22.766	25.721	1.00	51.17	B
ATOM	428	CG2	ILE	B	5	21.412	23.329	26.691	1.00	52.10	B
ATOM	429	CG1	ILE	B	5	21.871	21.592	24.917	1.00	52.55	B
ATOM	430	CD1	ILE	B	5	21.496	20.363	25.754	1.00	53.47	B
ATOM	431	C	ILE	B	5	23.452	25.043	25.600	1.00	53.54	B
ATOM	432	O	ILE	B	5	22.743	26.013	25.849	1.00	52.58	B
ATOM	433	N	GLU	B	6	24.701	24.932	26.036	1.00	55.54	B
ATOM	434	CA	GLU	B	6	25.309	25.970	26.850	1.00	56.11	B
ATOM	435	CB	GLU	B	6	26.637	25.477	27.437	1.00	53.75	B
ATOM	436	CG	GLU	B	6	26.487	24.157	28.171	1.00	53.07	B
ATOM	437	CD	GLU	B	6	27.729	23.735	28.939	1.00	50.56	B
ATOM	438	OE1	GLU	B	6	28.816	23.611	28.329	1.00	49.24	B
ATOM	439	OE2	GLU	B	6	27.604	23.516	30.159	1.00	47.31	B
ATOM	440	C	GLU	B	6	25.522	27.217	26.009	1.00	57.04	B
ATOM	441	O	GLU	B	6	25.418	28.335	26.515	1.00	58.94	B
ATOM	442	N	ASP	B	7	25.811	27.031	24.725	1.00	57.18	B
ATOM	443	CA	ASP	B	7	26.003	28.179	23.848	1.00	58.51	B
ATOM	444	CB	ASP	B	7	26.681	27.772	22.536	1.00	59.88	B
ATOM	445	CG	ASP	B	7	28.121	27.339	22.732	1.00	62.42	B
ATOM	446	OD1	ASP	B	7	28.827	27.979	23.542	1.00	62.53	B
ATOM	447	OD2	ASP	B	7	28.559	26.382	22.056	1.00	66.19	B
ATOM	448	C	ASP	B	7	24.668	28.858	23.543	1.00	58.25	B
ATOM	449	O	ASP	B	7	24.624	30.070	23.314	1.00	56.00	B
ATOM	450	N	LYS	B	8	23.591	28.069	23.547	1.00	57.96	B
ATOM	451	CA	LYS	B	8	22.240	28.563	23.276	1.00	57.58	B
ATOM	452	CB	LYS	B	8	21.331	27.405	22.838	1.00	57.99	B
ATOM	453	CG	LYS	B	8	19.911	27.844	22.484	1.00	60.08	B
ATOM	454	CD	LYS	B	8	19.915	28.785	21.280	1.00	60.12	B
ATOM	455	CE	LYS	B	8	18.697	29.725	21.268	1.00	60.76	B
ATOM	456	NZ	LYS	B	8	17.371	29.062	21.146	1.00	58.46	B
ATOM	457	C	LYS	B	8	21.653	29.248	24.517	1.00	56.86	B
ATOM	458	O	LYS	B	8	20.832	30.166	24.411	1.00	53.70	B
ATOM	459	N	ILE	B	9	22.077	28.790	25.689	1.00	57.87	B
ATOM	460	CA	ILE	B	9	21.621	29.368	26.947	1.00	59.31	B
ATOM	461	CB	ILE	B	9	22.073	28.517	28.161	1.00	57.40	B
ATOM	462	CG2	ILE	B	9	21.788	29.270	29.459	1.00	57.21	B
ATOM	463	CG1	ILE	B	9	21.361	27.165	28.154	1.00	56.21	B
ATOM	464	CD1	ILE	B	9	21.885	26.199	29.212	1.00	54.49	B
ATOM	465	C	ILE	B	9	22.216	30.770	27.093	1.00	60.74	B
ATOM	466	O	ILE	B	9	21.565	31.682	27.608	1.00	61.51	B
ATOM	467	N	GLU	B	10	23.456	30.923	26.633	1.00	61.69	B
ATOM	468	CA	GLU	B	10	24.170	32.198	26.691	1.00	63.76	B
ATOM	469	CB	GLU	B	10	25.629	32.000	26.279	1.00	63.63	B
ATOM	470	CG	GLU	B	10	26.456	33.275	26.254	1.00	65.58	B
ATOM	471	CD	GLU	B	10	27.854	33.054	25.707	1.00	66.48	B

Figure 11H

ATOM	472	OE1	GLU	B	10	27.979	32.751	24.499	1.00	67.38	B
ATOM	473	OE2	GLU	B	10	28.824	33.173	26.485	1.00	66.28	B
ATOM	474	C	GLU	B	10	23.515	33.211	25.757	1.00	65.16	B
ATOM	475	O	GLU	B	10	23.261	34.351	26.141	1.00	65.81	B
ATOM	476	N	GLU	B	11	23.255	32.785	24.524	1.00	66.64	B
ATOM	477	CA	GLU	B	11	22.617	33.637	23.529	1.00	67.59	B
ATOM	478	CB	GLU	B	11	22.348	32.832	22.252	1.00	68.72	B
ATOM	479	CG	GLU	B	11	21.735	33.636	21.117	1.00	72.88	B
ATOM	480	CD	GLU	B	11	22.556	34.864	20.767	1.00	74.80	B
ATOM	481	OE1	GLU	B	11	23.775	34.717	20.526	1.00	75.81	B
ATOM	482	OE2	GLU	B	11	21.978	35.975	20.731	1.00	74.99	B
ATOM	483	C	GLU	B	11	21.307	34.197	24.098	1.00	67.17	B
ATOM	484	O	GLU	B	11	20.998	35.381	23.918	1.00	68.06	B
ATOM	485	N	ILE	B	12	20.541	33.348	24.784	1.00	64.61	B
ATOM	486	CA	ILE	B	12	19.288	33.790	25.389	1.00	61.65	B
ATOM	487	CB	ILE	B	12	18.458	32.600	25.926	1.00	62.84	B
ATOM	488	CG2	ILE	B	12	17.416	33.094	26.940	1.00	62.63	B
ATOM	489	CG1	ILE	B	12	17.799	31.864	24.750	1.00	62.13	B
ATOM	490	CD1	ILE	B	12	16.910	30.698	25.156	1.00	61.39	B
ATOM	491	C	ILE	B	12	19.553	34.776	26.522	1.00	58.17	B
ATOM	492	O	ILE	B	12	19.010	35.881	26.523	1.00	55.05	B
ATOM	493	N	GLU	B	13	20.388	34.384	27.479	1.00	55.87	B
ATOM	494	CA	GLU	B	13	20.710	35.268	28.600	1.00	54.71	B
ATOM	495	CB	GLU	B	13	21.817	34.669	29.477	1.00	50.19	B
ATOM	496	CG	GLU	B	13	21.447	33.331	30.109	1.00	49.30	B
ATOM	497	CD	GLU	B	13	22.577	32.729	30.933	1.00	49.10	B
ATOM	498	OE1	GLU	B	13	23.741	32.765	30.472	1.00	50.79	B
ATOM	499	OE2	GLU	B	13	22.304	32.194	32.027	1.00	47.00	B
ATOM	500	C	GLU	B	13	21.166	36.612	28.047	1.00	55.57	B
ATOM	501	O	GLU	B	13	20.790	37.667	28.557	1.00	56.33	B
ATOM	502	N	SER	B	14	21.950	36.559	26.977	1.00	56.02	B
ATOM	503	CA	SER	B	14	22.468	37.763	26.350	1.00	55.71	B
ATOM	504	CB	SER	B	14	23.488	37.389	25.278	1.00	54.62	B
ATOM	505	OG	SER	B	14	23.968	38.550	24.629	1.00	56.74	B
ATOM	506	C	SER	B	14	21.366	38.624	25.736	1.00	55.96	B
ATOM	507	O	SER	B	14	21.469	39.854	25.696	1.00	54.91	B
ATOM	508	N	LYS	B	15	20.310	37.979	25.263	1.00	55.94	B
ATOM	509	CA	LYS	B	15	19.208	38.704	24.650	1.00	56.72	B
ATOM	510	CB	LYS	B	15	18.454	37.779	23.693	1.00	55.67	B
ATOM	511	CG	LYS	B	15	17.494	38.484	22.772	1.00	58.33	B
ATOM	512	CD	LYS	B	15	17.000	37.527	21.705	1.00	59.89	B
ATOM	513	CE	LYS	B	15	16.440	38.282	20.518	1.00	60.44	B
ATOM	514	NZ	LYS	B	15	16.020	37.375	19.412	1.00	63.67	B
ATOM	515	C	LYS	B	15	18.282	39.207	25.748	1.00	56.31	B
ATOM	516	O	LYS	B	15	17.716	40.296	25.661	1.00	56.65	B
ATOM	517	N	GLN	B	16	18.146	38.403	26.791	1.00	56.76	B
ATOM	518	CA	GLN	B	16	17.293	38.748	27.911	1.00	57.28	B
ATOM	519	CB	GLN	B	16	17.306	37.604	28.923	1.00	56.94	B
ATOM	520	CG	GLN	B	16	16.000	37.394	29.652	1.00	55.90	B
ATOM	521	CD	GLN	B	16	15.908	36.017	30.300	1.00	56.24	B
ATOM	522	OE1	GLN	B	16	16.613	35.722	31.263	1.00	57.78	B
ATOM	523	NE2	GLN	B	16	15.044	35.160	29.760	1.00	55.69	B
ATOM	524	C	GLN	B	16	17.825	40.040	28.528	1.00	58.82	B
ATOM	525	O	GLN	B	16	17.049	40.929	28.905	1.00	59.68	B
ATOM	526	N	LYS	B	17	19.148	40.163	28.621	1.00	59.44	B
ATOM	527	CA	LYS	B	17	19.711	41.379	29.189	1.00	59.84	B
ATOM	528	CB	LYS	B	17	21.229	41.275	29.386	1.00	60.80	B
ATOM	529	CG	LYS	B	17	21.740	42.343	30.356	1.00	64.52	B
ATOM	530	CD	LYS	B	17	23.250	42.325	30.576	1.00	65.30	B
ATOM	531	CE	LYS	B	17	24.008	42.784	29.344	1.00	67.22	B

Figure 11I

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ATOM    532  NZ  LYS B  17      25.465  42.963  29.625  1.00 67.09      B
ATOM    533  C   LYS B  17      19.389  42.522  28.230  1.00 59.16      B
ATOM    534  O   LYS B  17      19.088  43.634  28.656  1.00 55.77      B
ATOM    535  N   LYS B  18      19.433  42.233  26.931  1.00 58.38      B
ATOM    536  CA  LYS B  18      19.128  43.248  25.931  1.00 58.35      B
ATOM    537  CB  LYS B  18      19.247  42.675  24.511  1.00 59.38      B
ATOM    538  CG  LYS B  18      20.617  42.083  24.130  1.00 61.47      B
ATOM    539  CD  LYS B  18      21.768  43.111  24.099  1.00 61.91      B
ATOM    540  CE  LYS B  18      22.034  43.761  25.461  1.00 63.50      B
ATOM    541  NZ  LYS B  18      23.248  44.620  25.423  1.00 63.66      B
ATOM    542  C   LYS B  18      17.706  43.761  26.163  1.00 58.27      B
ATOM    543  O   LYS B  18      17.475  44.969  26.254  1.00 58.82      B
ATOM    544  N   ILE B  19      16.757  42.825  26.268  1.00 56.89      B
ATOM    545  CA  ILE B  19      15.356  43.189  26.488  1.00 53.76      B
ATOM    546  CB  ILE B  19      14.455  41.931  26.488  1.00 53.33      B
ATOM    547  CG2 ILE B  19      13.057  42.286  26.976  1.00 52.66      B
ATOM    548  CG1 ILE B  19      14.416  41.322  25.081  1.00 52.79      B
ATOM    549  CD1 ILE B  19      13.543  40.069  24.970  1.00 54.45      B
ATOM    550  C   ILE B  19      15.117  43.961  27.786  1.00 52.88      B
ATOM    551  O   ILE B  19      14.327  44.897  27.809  1.00 51.74      B
ATOM    552  N   GLU B  20      15.781  43.565  28.869  1.00 51.04      B
ATOM    553  CA  GLU B  20      15.601  44.267  30.128  1.00 50.08      B
ATOM    554  CB  GLU B  20      16.403  43.613  31.253  1.00 49.90      B
ATOM    555  CG  GLU B  20      15.969  42.207  31.584  1.00 54.19      B
ATOM    556  CD  GLU B  20      16.761  41.620  32.736  1.00 55.98      B
ATOM    557  OE1 GLU B  20      18.010  41.568  32.641  1.00 53.23      B
ATOM    558  OE2 GLU B  20      16.127  41.215  33.735  1.00 56.20      B
ATOM    559  C   GLU B  20      16.053  45.706  29.965  1.00 49.26      B
ATOM    560  O   GLU B  20      15.479  46.611  30.561  1.00 48.88      B
ATOM    561  N   ASN B  21      17.093  45.912  29.163  1.00 49.15      B
ATOM    562  CA  ASN B  21      17.596  47.256  28.930  1.00 49.99      B
ATOM    563  CB  ASN B  21      18.885  47.229  28.098  1.00 51.35      B
ATOM    564  CG  ASN B  21      20.054  46.576  28.834  1.00 54.79      B
ATOM    565  OD1 ASN B  21      20.421  46.978  29.943  1.00 55.96      B
ATOM    566  ND2 ASN B  21      20.656  45.572  28.205  1.00 57.15      B
ATOM    567  C   ASN B  21      16.537  48.078  28.202  1.00 49.83      B
ATOM    568  O   ASN B  21      16.249  49.209  28.591  1.00 50.14      B
ATOM    569  N   GLU B  22      15.957  47.497  27.153  1.00 47.34      B
ATOM    570  CA  GLU B  22      14.942  48.160  26.354  1.00 44.99      B
ATOM    571  CB  GLU B  22      14.534  47.272  25.174  1.00 44.99      B
ATOM    572  CG  GLU B  22      13.703  47.990  24.116  1.00 51.85      B
ATOM    573  CD  GLU B  22      14.377  49.268  23.621  1.00 54.71      B
ATOM    574  OE1 GLU B  22      15.543  49.191  23.182  1.00 55.60      B
ATOM    575  OE2 GLU B  22      13.743  50.350  23.673  1.00 57.01      B
ATOM    576  C   GLU B  22      13.710  48.521  27.183  1.00 44.17      B
ATOM    577  O   GLU B  22      13.044  49.527  26.916  1.00 45.50      B
ATOM    578  N   ILE B  23      13.386  47.693  28.169  1.00 42.28      B
ATOM    579  CA  ILE B  23      12.241  47.977  29.024  1.00 40.61      B
ATOM    580  CB  ILE B  23      11.801  46.724  29.809  1.00 38.57      B
ATOM    581  CG2 ILE B  23      10.836  47.096  30.925  1.00 37.31      B
ATOM    582  CG1 ILE B  23      11.138  45.733  28.850  1.00 38.28      B
ATOM    583  CD1 ILE B  23      10.634  44.436  29.530  1.00 38.32      B
ATOM    584  C   ILE B  23      12.626  49.108  29.974  1.00 41.50      B
ATOM    585  O   ILE B  23      11.793  49.926  30.349  1.00 41.54      B
ATOM    586  N   ALA B  24      13.898  49.170  30.348  1.00 40.42      B
ATOM    587  CA  ALA B  24      14.349  50.240  31.224  1.00 38.49      B
ATOM    588  CB  ALA B  24      15.811  50.059  31.578  1.00 34.26      B
ATOM    589  C   ALA B  24      14.147  51.562  30.490  1.00 37.76      B
ATOM    590  O   ALA B  24      13.674  52.528  31.078  1.00 38.39      B
ATOM    591  N   ARG B  25      14.498  51.591  29.204  1.00 36.47      B
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Figure 11J

ATOM	592	CA	ARG	B	25	14.354	52.796	28.394	1.00	38.10	B
ATOM	593	CB	ARG	B	25	15.086	52.644	27.051	1.00	40.70	B
ATOM	594	CG	ARG	B	25	16.609	52.668	27.195	1.00	46.74	B
ATOM	595	CD	ARG	B	25	17.315	52.949	25.879	1.00	51.86	B
ATOM	596	NE	ARG	B	25	17.268	51.823	24.954	1.00	56.83	B
ATOM	597	CZ	ARG	B	25	17.894	50.666	25.152	1.00	59.56	B
ATOM	598	NH1	ARG	B	25	18.615	50.477	26.253	1.00	60.08	B
ATOM	599	NH2	ARG	B	25	17.792	49.696	24.257	1.00	59.81	B
ATOM	600	C	ARG	B	25	12.901	53.185	28.158	1.00	36.71	B
ATOM	601	O	ARG	B	25	12.555	54.361	28.165	1.00	36.54	B
ATOM	602	N	ILE	B	26	12.051	52.197	27.942	1.00	36.23	B
ATOM	603	CA	ILE	B	26	10.642	52.454	27.733	1.00	34.33	B
ATOM	604	CB	ILE	B	26	9.944	51.152	27.370	1.00	34.16	B
ATOM	605	CG2	ILE	B	26	8.432	51.293	27.496	1.00	31.45	B
ATOM	606	CG1	ILE	B	26	10.423	50.722	25.985	1.00	34.01	B
ATOM	607	CD1	ILE	B	26	9.879	49.403	25.540	1.00	34.37	B
ATOM	608	C	ILE	B	26	10.046	53.059	29.005	1.00	34.32	B
ATOM	609	O	ILE	B	26	9.317	54.053	28.956	1.00	33.13	B
ATOM	610	N	LYS	B	27	10.371	52.457	30.141	1.00	34.59	B
ATOM	611	CA	LYS	B	27	9.898	52.941	31.433	1.00	35.31	B
ATOM	612	CB	LYS	B	27	10.366	52.005	32.544	1.00	36.43	B
ATOM	613	CG	LYS	B	27	9.398	50.872	32.885	1.00	40.24	B
ATOM	614	CD	LYS	B	27	10.162	49.643	33.347	1.00	44.60	B
ATOM	615	CE	LYS	B	27	11.278	49.991	34.334	1.00	50.65	B
ATOM	616	NZ	LYS	B	27	12.209	48.831	34.560	1.00	54.97	B
ATOM	617	C	LYS	B	27	10.382	54.355	31.712	1.00	35.58	B
ATOM	618	O	LYS	B	27	9.666	55.140	32.318	1.00	36.82	B
ATOM	619	N	LYS	B	28	11.599	54.670	31.268	1.00	36.91	B
ATOM	620	CA	LYS	B	28	12.189	55.993	31.463	1.00	37.71	B
ATOM	621	CB	LYS	B	28	13.627	56.017	30.958	1.00	42.60	B
ATOM	622	CG	LYS	B	28	14.604	56.755	31.851	1.00	49.26	B
ATOM	623	CD	LYS	B	28	15.299	55.778	32.818	1.00	55.52	B
ATOM	624	CE	LYS	B	28	14.318	54.979	33.680	1.00	58.79	B
ATOM	625	NZ	LYS	B	28	15.015	53.887	34.421	1.00	59.10	B
ATOM	626	C	LYS	B	28	11.397	57.044	30.677	1.00	37.60	B
ATOM	627	O	LYS	B	28	10.956	58.045	31.240	1.00	40.12	B
ATOM	628	N	LEU	B	29	11.250	56.826	29.368	1.00	35.33	B
ATOM	629	CA	LEU	B	29	10.515	57.754	28.524	1.00	35.90	B
ATOM	630	CB	LEU	B	29	10.440	57.267	27.071	1.00	36.49	B
ATOM	631	CG	LEU	B	29	9.495	58.127	26.202	1.00	37.58	B
ATOM	632	CD1	LEU	B	29	9.958	59.581	26.260	1.00	36.39	B
ATOM	633	CD2	LEU	B	29	9.441	57.641	24.744	1.00	35.00	B
ATOM	634	C	LEU	B	29	9.103	57.912	29.047	1.00	35.09	B
ATOM	635	O	LEU	B	29	8.568	59.015	29.095	1.00	34.76	B
ATOM	636	N	LEU	B	30	8.512	56.787	29.426	1.00	33.74	B
ATOM	637	CA	LEU	B	30	7.161	56.746	29.946	1.00	30.65	B
ATOM	638	CB	LEU	B	30	6.789	55.284	30.181	1.00	32.72	B
ATOM	639	CG	LEU	B	30	5.385	54.822	30.558	1.00	31.65	B
ATOM	640	CD1	LEU	B	30	4.353	55.404	29.599	1.00	34.37	B
ATOM	641	CD2	LEU	B	30	5.377	53.282	30.511	1.00	31.69	B
ATOM	642	C	LEU	B	30	6.985	57.588	31.213	1.00	31.56	B
ATOM	643	O	LEU	B	30	6.051	58.398	31.301	1.00	26.54	B
ATOM	644	N	GLN	B	31	7.860	57.442	32.206	1.00	31.24	B
ATOM	645	CA	GLN	B	31	7.668	58.265	33.398	1.00	33.01	B
ATOM	646	CB	GLN	B	31	8.551	57.801	34.564	1.00	33.79	B
ATOM	647	CG	GLN	B	31	10.013	57.729	34.321	1.00	40.81	B
ATOM	648	CD	GLN	B	31	10.737	57.086	35.491	1.00	44.04	B
ATOM	649	OE1	GLN	B	31	10.804	57.648	36.598	1.00	43.99	B
ATOM	650	NE2	GLN	B	31	11.270	55.889	35.258	1.00	41.97	B
ATOM	651	C	GLN	B	31	7.906	59.734	33.072	1.00	34.12	B

Figure 11K

ATOM	652	O	GLN	B	31	7.420	60.636	33.766	1.00	30.63	B
ATOM	653	N	LEU	B	32	8.629	59.961	31.984	1.00	34.46	B
ATOM	654	CA	LEU	B	32	8.935	61.292	31.523	1.00	36.10	B
ATOM	655	CB	LEU	B	32	10.070	61.231	30.504	1.00	40.01	B
ATOM	656	CG	LEU	B	32	10.340	62.546	29.775	1.00	40.15	B
ATOM	657	CD1	LEU	B	32	10.853	63.586	30.765	1.00	43.23	B
ATOM	658	CD2	LEU	B	32	11.354	62.310	28.668	1.00	43.00	B
ATOM	659	C	LEU	B	32	7.711	61.949	30.890	1.00	36.08	B
ATOM	660	O	LEU	B	32	7.552	63.162	30.964	1.00	37.71	B
ATOM	661	N	THR	B	33	6.859	61.149	30.255	1.00	32.40	B
ATOM	662	CA	THR	B	33	5.659	61.679	29.617	1.00	31.31	B
ATOM	663	CB	THR	B	33	5.179	60.753	28.480	1.00	30.70	B
ATOM	664	OG1	THR	B	33	4.536	59.603	29.030	1.00	40.03	B
ATOM	665	CG2	THR	B	33	6.371	60.282	27.654	1.00	31.28	B
ATOM	666	C	THR	B	33	4.550	61.845	30.668	1.00	30.03	B
ATOM	667	O	THR	B	33	3.739	62.772	30.585	1.00	30.10	B
ATOM	668	N	VAL	B	34	4.507	60.933	31.636	1.00	27.29	B
ATOM	669	CA	VAL	B	34	3.546	61.010	32.735	1.00	25.28	B
ATOM	670	CB	VAL	B	34	3.695	59.806	33.690	1.00	26.71	B
ATOM	671	CG1	VAL	B	34	2.920	60.036	34.985	1.00	27.25	B
ATOM	672	CG2	VAL	B	34	3.176	58.565	32.997	1.00	23.84	B
ATOM	673	C	VAL	B	34	3.822	62.310	33.476	1.00	22.65	B
ATOM	674	O	VAL	B	34	2.899	63.064	33.763	1.00	21.36	B
ATOM	675	N	TRP	B	35	5.100	62.580	33.757	1.00	22.24	B
ATOM	676	CA	TRP	B	35	5.502	63.828	34.414	1.00	20.87	B
ATOM	677	CB	TRP	B	35	7.016	63.843	34.653	1.00	23.71	B
ATOM	678	CG	TRP	B	35	7.523	65.040	35.434	1.00	26.08	B
ATOM	679	CD2	TRP	B	35	7.013	65.551	36.681	1.00	25.13	B
ATOM	680	CE2	TRP	B	35	7.767	66.698	37.003	1.00	28.35	B
ATOM	681	CE3	TRP	B	35	5.985	65.143	37.547	1.00	24.83	B
ATOM	682	CD1	TRP	B	35	8.540	65.880	35.074	1.00	25.67	B
ATOM	683	NE1	TRP	B	35	8.692	66.877	36.006	1.00	27.74	B
ATOM	684	CZ2	TRP	B	35	7.532	67.455	38.165	1.00	28.38	B
ATOM	685	CZ3	TRP	B	35	5.749	65.889	38.699	1.00	23.47	B
ATOM	686	CH2	TRP	B	35	6.516	67.034	38.999	1.00	28.31	B
ATOM	687	C	TRP	B	35	5.121	65.039	33.564	1.00	24.26	B
ATOM	688	O	TRP	B	35	4.695	66.063	34.088	1.00	23.94	B
ATOM	689	N	GLY	B	36	5.308	64.927	32.247	1.00	25.59	B
ATOM	690	CA	GLY	B	36	4.961	66.013	31.348	1.00	23.22	B
ATOM	691	C	GLY	B	36	3.479	66.364	31.343	1.00	25.72	B
ATOM	692	O	GLY	B	36	3.138	67.539	31.352	1.00	28.94	B
ATOM	693	N	ILE	B	37	2.610	65.356	31.311	1.00	27.20	B
ATOM	694	CA	ILE	B	37	1.160	65.560	31.315	1.00	24.67	B
ATOM	695	CB	ILE	B	37	0.429	64.223	31.230	1.00	24.72	B
ATOM	696	CG2	ILE	B	37	-1.085	64.410	31.416	1.00	29.15	B
ATOM	697	CG1	ILE	B	37	0.700	63.581	29.879	1.00	22.40	B
ATOM	698	CD1	ILE	B	37	0.023	62.237	29.714	1.00	24.46	B
ATOM	699	C	ILE	B	37	0.734	66.295	32.579	1.00	25.86	B
ATOM	700	O	ILE	B	37	-0.019	67.255	32.517	1.00	25.23	B
ATOM	701	N	LYS	B	38	1.242	65.840	33.722	1.00	26.17	B
ATOM	702	CA	LYS	B	38	0.967	66.449	35.020	1.00	22.96	B
ATOM	703	CB	LYS	B	38	1.656	65.652	36.130	1.00	22.07	B
ATOM	704	CG	LYS	B	38	0.953	64.410	36.522	1.00	25.14	B
ATOM	705	CD	LYS	B	38	-0.225	64.727	37.423	1.00	28.48	B
ATOM	706	CE	LYS	B	38	-1.014	63.468	37.617	1.00	28.77	B
ATOM	707	NZ	LYS	B	38	-1.331	62.953	36.269	1.00	34.06	B
ATOM	708	C	LYS	B	38	1.458	67.877	35.102	1.00	23.87	B
ATOM	709	O	LYS	B	38	0.770	68.736	35.640	1.00	20.93	B
ATOM	710	N	GLN	B	39	2.662	68.140	34.593	1.00	26.53	B
ATOM	711	CA	GLN	B	39	3.189	69.493	34.682	1.00	30.76	B

Figure 11L

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ATOM    712  CB  GLN B  39       4.629  69.583  34.197  1.00 33.05      B
ATOM    713  CG  GLN B  39       5.436  70.614  34.985  1.00 43.49      B
ATOM    714  CD  GLN B  39       4.822  72.026  35.008  1.00 48.65      B
ATOM    715  OE1 GLN B  39       4.889  72.774  34.021  1.00 51.46      B
ATOM    716  NE2 GLN B  39       4.220  72.389  36.143  1.00 47.35      B
ATOM    717  C   GLN B  39       2.343  70.417  33.843  1.00 31.81      B
ATOM    718  O   GLN B  39       2.125  71.574  34.206  1.00 31.08      B
ATOM    719  N   LEU B  40       1.897  69.904  32.703  1.00 31.01      B
ATOM    720  CA  LEU B  40       1.065  70.671  31.807  1.00 33.41      B
ATOM    721  CB  LEU B  40       0.872  69.886  30.517  1.00 32.63      B
ATOM    722  CG  LEU B  40      -0.126  70.405  29.482  1.00 34.65      B
ATOM    723  CD1 LEU B  40       0.171  71.843  29.092  1.00 35.24      B
ATOM    724  CD2 LEU B  40      -0.058  69.495  28.281  1.00 35.90      B
ATOM    725  C   LEU B  40      -0.289  70.943  32.469  1.00 36.85      B
ATOM    726  O   LEU B  40      -0.874  72.010  32.314  1.00 37.81      B
ATOM    727  N   GLN B  41      -0.768  69.964  33.215  1.00 36.13      B
ATOM    728  CA  GLN B  41      -2.046  70.063  33.894  1.00 37.74      B
ATOM    729  CB  GLN B  41      -2.369  68.718  34.517  1.00 41.31      B
ATOM    730  CG  GLN B  41      -3.833  68.459  34.735  1.00 47.08      B
ATOM    731  CD  GLN B  41      -4.070  67.139  35.420  1.00 54.09      B
ATOM    732  OE1 GLN B  41      -3.517  66.102  35.013  1.00 55.42      B
ATOM    733  NE2 GLN B  41      -4.908  67.154  36.461  1.00 54.90      B
ATOM    734  C   GLN B  41      -2.039  71.148  34.974  1.00 39.95      B
ATOM    735  O   GLN B  41      -2.988  71.925  35.089  1.00 39.23      B
ATOM    736  N   ALA B  42      -0.972  71.194  35.767  1.00 39.05      B
ATOM    737  CA  ALA B  42      -0.845  72.188  36.824  1.00 38.56      B
ATOM    738  CB  ALA B  42       0.345  71.852  37.757  1.00 34.14      B
ATOM    739  C   ALA B  42      -0.647  73.566  36.228  1.00 40.18      B
ATOM    740  O   ALA B  42      -1.139  74.560  36.765  1.00 41.44      B
ATOM    741  N   ARG B  43       0.078  73.634  35.118  1.00 41.82      B
ATOM    742  CA  ARG B  43       0.340  74.910  34.476  1.00 43.71      B
ATOM    743  CB  ARG B  43       1.242  74.713  33.260  1.00 47.26      B
ATOM    744  CG  ARG B  43       1.703  75.997  32.592  1.00 51.08      B
ATOM    745  CD  ARG B  43       2.582  75.677  31.401  1.00 54.95      B
ATOM    746  NE  ARG B  43       3.778  74.947  31.813  1.00 57.04      B
ATOM    747  CZ  ARG B  43       4.819  75.499  32.428  1.00 56.95      B
ATOM    748  NH1 ARG B  43       4.816  76.794  32.703  1.00 55.89      B
ATOM    749  NH2 ARG B  43       5.858  74.753  32.781  1.00 57.00      B
ATOM    750  C   ARG B  43      -0.987  75.521  34.048  1.00 42.38      B
ATOM    751  O   ARG B  43      -1.308  76.657  34.398  1.00 41.41      B
ATOM    752  N   ILE B  44      -1.756  74.736  33.310  1.00 41.63      B
ATOM    753  CA  ILE B  44      -3.059  75.143  32.810  1.00 43.24      B
ATOM    754  CB  ILE B  44      -3.634  74.085  31.866  1.00 44.23      B
ATOM    755  CG2 ILE B  44      -5.083  74.403  31.592  1.00 45.04      B
ATOM    756  CG1 ILE B  44      -2.778  73.964  30.600  1.00 47.45      B
ATOM    757  CD1 ILE B  44      -3.156  72.745  29.719  1.00 49.42      B
ATOM    758  C   ILE B  44      -4.081  75.306  33.935  1.00 42.37      B
ATOM    759  O   ILE B  44      -4.422  76.416  34.332  1.00 42.08      B
ATOM    760  N   LEU B  45      -4.573  74.162  34.398  1.00 42.20      B
ATOM    761  CA  LEU B  45      -5.564  74.042  35.450  1.00 43.16      B
ATOM    762  CB  LEU B  45      -6.041  72.592  35.513  1.00 46.08      B
ATOM    763  CG  LEU B  45      -6.459  72.001  34.162  1.00 47.45      B
ATOM    764  CD1 LEU B  45      -7.011  70.594  34.357  1.00 47.51      B
ATOM    765  CD2 LEU B  45      -7.504  72.899  33.521  1.00 48.61      B
ATOM    766  C   LEU B  45      -5.016  74.467  36.810  1.00 42.48      B
ATOM    767  O   LEU B  45      -5.674  75.260  37.483  1.00 45.15      B
ATOM    768  NT  LEU B  45      -3.945  73.987  37.206  1.00 45.66      B
ATOM    769  CA  ACE C   0      15.143  11.286  26.819  1.00 82.49      C
ATOM    770  C   ACE C   0      14.856  12.476  27.674  1.00 82.44      C
ATOM    771  O   ACE C   0      13.700  12.858  27.851  1.00 84.06      C
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Figure 11M

ATOM	772	N	ARG	C	1	15.890	13.103	28.220	1.00	83.91	C
ATOM	773	CA	ARG	C	1	15.663	14.253	29.073	1.00	83.87	C
ATOM	774	CB	ARG	C	1	16.156	13.970	30.491	1.00	83.74	C
ATOM	775	CG	ARG	C	1	15.769	15.065	31.456	1.00	83.47	C
ATOM	776	CD	ARG	C	1	14.340	15.542	31.156	1.00	81.66	C
ATOM	777	NE	ARG	C	1	13.249	14.748	31.726	1.00	81.00	C
ATOM	778	CZ	ARG	C	1	13.069	13.434	31.597	1.00	79.16	C
ATOM	779	NH1	ARG	C	1	13.901	12.678	30.889	1.00	79.80	C
ATOM	780	NH2	ARG	C	1	12.010	12.875	32.168	1.00	79.18	C
ATOM	781	C	ARG	C	1	16.282	15.541	28.550	1.00	85.03	C
ATOM	782	O	ARG	C	1	15.975	16.644	29.016	1.00	85.10	C
ATOM	783	N	MET	C	2	17.169	15.394	27.581	1.00	85.40	C
ATOM	784	CA	MET	C	2	17.778	16.568	27.012	1.00	86.91	C
ATOM	785	CB	MET	C	2	19.063	16.215	26.290	1.00	88.20	C
ATOM	786	CG	MET	C	2	19.711	17.410	25.653	1.00	89.72	C
ATOM	787	SD	MET	C	2	21.192	16.917	24.823	1.00	94.98	C
ATOM	788	CE	MET	C	2	22.111	16.349	26.176	1.00	91.53	C
ATOM	789	C	MET	C	2	16.771	17.154	26.036	1.00	87.44	C
ATOM	790	O	MET	C	2	16.699	18.368	25.872	1.00	89.05	C
ATOM	791	N	LYS	C	3	16.001	16.278	25.391	1.00	85.66	C
ATOM	792	CA	LYS	C	3	14.973	16.712	24.444	1.00	83.09	C
ATOM	793	CB	LYS	C	3	14.033	15.551	24.107	1.00	82.50	C
ATOM	794	CG	LYS	C	3	12.921	15.895	23.122	1.00	81.54	C
ATOM	795	CD	LYS	C	3	11.926	14.746	23.005	1.00	81.93	C
ATOM	796	CE	LYS	C	3	10.866	15.022	21.952	1.00	80.79	C
ATOM	797	NZ	LYS	C	3	10.154	16.300	22.214	1.00	82.56	C
ATOM	798	C	LYS	C	3	14.177	17.809	25.128	1.00	82.12	C
ATOM	799	O	LYS	C	3	14.053	18.925	24.617	1.00	81.76	C
ATOM	800	N	GLN	C	4	13.651	17.474	26.302	1.00	80.32	C
ATOM	801	CA	GLN	C	4	12.856	18.401	27.094	1.00	78.87	C
ATOM	802	CB	GLN	C	4	12.504	17.759	28.440	1.00	79.91	C
ATOM	803	CG	GLN	C	4	12.122	16.275	28.356	1.00	80.66	C
ATOM	804	CD	GLN	C	4	11.087	15.971	27.280	1.00	81.02	C
ATOM	805	OE1	GLN	C	4	11.348	16.140	26.082	1.00	79.52	C
ATOM	806	NE2	GLN	C	4	9.907	15.516	27.701	1.00	81.57	C
ATOM	807	C	GLN	C	4	13.667	19.680	27.299	1.00	77.97	C
ATOM	808	O	GLN	C	4	13.186	20.781	27.032	1.00	78.45	C
ATOM	809	N	ILE	C	5	14.902	19.530	27.772	1.00	76.07	C
ATOM	810	CA	ILE	C	5	15.785	20.670	27.974	1.00	73.89	C
ATOM	811	CB	ILE	C	5	17.206	20.220	28.381	1.00	73.07	C
ATOM	812	CG2	ILE	C	5	18.175	21.388	28.264	1.00	71.17	C
ATOM	813	CG1	ILE	C	5	17.174	19.623	29.795	1.00	72.84	C
ATOM	814	CD1	ILE	C	5	18.518	19.113	30.285	1.00	71.39	C
ATOM	815	C	ILE	C	5	15.880	21.423	26.656	1.00	74.14	C
ATOM	816	O	ILE	C	5	15.939	22.651	26.628	1.00	73.70	C
ATOM	817	N	GLU	C	6	15.895	20.664	25.567	1.00	73.88	C
ATOM	818	CA	GLU	C	6	15.972	21.222	24.225	1.00	73.70	C
ATOM	819	CB	GLU	C	6	16.395	20.135	23.229	1.00	72.24	C
ATOM	820	CG	GLU	C	6	17.787	19.535	23.464	1.00	69.96	C
ATOM	821	CD	GLU	C	6	18.922	20.428	22.985	1.00	68.01	C
ATOM	822	OE1	GLU	C	6	19.044	21.575	23.461	1.00	65.93	C
ATOM	823	OE2	GLU	C	6	19.702	19.963	22.125	1.00	68.18	C
ATOM	824	C	GLU	C	6	14.602	21.773	23.842	1.00	74.50	C
ATOM	825	O	GLU	C	6	14.476	22.546	22.890	1.00	75.27	C
ATOM	826	N	ASP	C	7	13.577	21.372	24.587	1.00	74.82	C
ATOM	827	CA	ASP	C	7	12.218	21.838	24.327	1.00	76.17	C
ATOM	828	CB	ASP	C	7	11.195	20.742	24.644	1.00	77.40	C
ATOM	829	CG	ASP	C	7	11.408	19.488	23.818	1.00	78.45	C
ATOM	830	OD1	ASP	C	7	11.518	19.609	22.580	1.00	79.26	C
ATOM	831	OD2	ASP	C	7	11.452	18.380	24.404	1.00	79.10	C

Figure 11N

ATOM	832	C	ASP	C	7	11.906	23.079	25.160	1.00	75.92	C
ATOM	833	O	ASP	C	7	11.379	24.063	24.643	1.00	77.15	C
ATOM	834	N	LYS	C	8	12.223	23.024	26.452	1.00	74.05	C
ATOM	835	CA	LYS	C	8	11.987	24.157	27.336	1.00	71.19	C
ATOM	836	CB	LYS	C	8	12.565	23.886	28.727	1.00	72.69	C
ATOM	837	CG	LYS	C	8	11.647	24.225	29.901	1.00	72.96	C
ATOM	838	CD	LYS	C	8	10.428	23.312	29.921	1.00	75.00	C
ATOM	839	CE	LYS	C	8	9.587	23.471	31.197	1.00	76.69	C
ATOM	840	NZ	LYS	C	8	8.998	24.829	31.389	1.00	73.68	C
ATOM	841	C	LYS	C	8	12.727	25.319	26.679	1.00	69.24	C
ATOM	842	O	LYS	C	8	12.295	26.469	26.745	1.00	69.77	C
ATOM	843	N	ILE	C	9	13.855	25.013	26.046	1.00	65.63	C
ATOM	844	CA	ILE	C	9	14.609	26.053	25.362	1.00	64.27	C
ATOM	845	CB	ILE	C	9	15.950	25.511	24.812	1.00	62.88	C
ATOM	846	CG2	ILE	C	9	16.585	26.515	23.871	1.00	62.42	C
ATOM	847	CG1	ILE	C	9	16.900	25.231	25.976	1.00	64.19	C
ATOM	848	CD1	ILE	C	9	18.244	24.656	25.557	1.00	64.32	C
ATOM	849	C	ILE	C	9	13.756	26.605	24.223	1.00	63.69	C
ATOM	850	O	ILE	C	9	13.735	27.816	23.985	1.00	63.21	C
ATOM	851	N	GLU	C	10	13.036	25.712	23.543	1.00	62.89	C
ATOM	852	CA	GLU	C	10	12.163	26.092	22.429	1.00	62.21	C
ATOM	853	CB	GLU	C	10	11.419	24.865	21.886	1.00	63.68	C
ATOM	854	CG	GLU	C	10	10.451	25.180	20.751	1.00	66.12	C
ATOM	855	CD	GLU	C	10	9.688	23.961	20.251	1.00	67.29	C
ATOM	856	OE1	GLU	C	10	8.874	24.125	19.318	1.00	69.26	C
ATOM	857	OE2	GLU	C	10	9.894	22.845	20.780	1.00	68.71	C
ATOM	858	C	GLU	C	10	11.142	27.147	22.831	1.00	60.65	C
ATOM	859	O	GLU	C	10	10.991	28.157	22.147	1.00	60.16	C
ATOM	860	N	GLU	C	11	10.429	26.898	23.927	1.00	60.41	C
ATOM	861	CA	GLU	C	11	9.415	27.826	24.435	1.00	58.98	C
ATOM	862	CB	GLU	C	11	8.736	27.243	25.683	1.00	59.35	C
ATOM	863	CG	GLU	C	11	9.709	26.588	26.652	1.00	61.78	C
ATOM	864	CD	GLU	C	11	9.376	26.801	28.127	1.00	63.00	C
ATOM	865	OE1	GLU	C	11	9.329	27.972	28.563	1.00	64.82	C
ATOM	866	OE2	GLU	C	11	9.184	25.804	28.855	1.00	60.50	C
ATOM	867	C	GLU	C	11	10.021	29.186	24.772	1.00	58.03	C
ATOM	868	O	GLU	C	11	9.519	30.229	24.351	1.00	59.21	C
ATOM	869	N	ILE	C	12	11.103	29.178	25.532	1.00	56.15	C
ATOM	870	CA	ILE	C	12	11.765	30.415	25.902	1.00	56.41	C
ATOM	871	CB	ILE	C	12	13.043	30.139	26.710	1.00	55.29	C
ATOM	872	CG2	ILE	C	12	13.791	31.448	26.950	1.00	52.26	C
ATOM	873	CG1	ILE	C	12	12.680	29.404	28.008	1.00	55.06	C
ATOM	874	CD1	ILE	C	12	13.858	29.085	28.914	1.00	55.11	C
ATOM	875	C	ILE	C	12	12.132	31.239	24.671	1.00	57.76	C
ATOM	876	O	ILE	C	12	11.944	32.454	24.659	1.00	59.18	C
ATOM	877	N	GLU	C	13	12.668	30.589	23.642	1.00	60.62	C
ATOM	878	CA	GLU	C	13	13.039	31.312	22.423	1.00	62.64	C
ATOM	879	CB	GLU	C	13	13.916	30.449	21.497	1.00	66.02	C
ATOM	880	CG	GLU	C	13	13.319	29.091	21.138	1.00	70.85	C
ATOM	881	CD	GLU	C	13	14.091	28.355	20.041	1.00	73.58	C
ATOM	882	OE1	GLU	C	13	15.330	28.233	20.163	1.00	72.99	C
ATOM	883	OE2	GLU	C	13	13.456	27.887	19.064	1.00	73.78	C
ATOM	884	C	GLU	C	13	11.785	31.748	21.679	1.00	60.74	C
ATOM	885	O	GLU	C	13	11.808	32.733	20.946	1.00	61.13	C
ATOM	886	N	SER	C	14	10.695	31.010	21.864	1.00	59.71	C
ATOM	887	CA	SER	C	14	9.432	31.350	21.211	1.00	60.53	C
ATOM	888	CB	SER	C	14	8.392	30.248	21.439	1.00	59.88	C
ATOM	889	OG	SER	C	14	7.157	30.571	20.820	1.00	56.34	C
ATOM	890	C	SER	C	14	8.921	32.668	21.790	1.00	61.04	C
ATOM	891	O	SER	C	14	8.793	33.655	21.073	1.00	59.08	C

Figure 11O

ATOM	892	N	LYS	C	15	8.632	32.671	23.091	1.00	62.79	C
ATOM	893	CA	LYS	C	15	8.153	33.873	23.771	1.00	64.30	C
ATOM	894	CB	LYS	C	15	7.949	33.612	25.273	1.00	65.74	C
ATOM	895	CG	LYS	C	15	6.637	32.903	25.642	1.00	68.25	C
ATOM	896	CD	LYS	C	15	6.534	32.695	27.154	1.00	69.92	C
ATOM	897	CE	LYS	C	15	5.186	32.131	27.564	1.00	70.69	C
ATOM	898	NZ	LYS	C	15	4.078	33.079	27.241	1.00	73.69	C
ATOM	899	C	LYS	C	15	9.130	35.029	23.601	1.00	64.03	C
ATOM	900	O	LYS	C	15	8.723	36.175	23.408	1.00	64.04	C
ATOM	901	N	GLN	C	16	10.418	34.721	23.678	1.00	63.47	C
ATOM	902	CA	GLN	C	16	11.451	35.733	23.537	1.00	65.82	C
ATOM	903	CB	GLN	C	16	12.813	35.064	23.393	1.00	65.17	C
ATOM	904	CG	GLN	C	16	13.970	36.027	23.413	1.00	65.29	C
ATOM	905	CD	GLN	C	16	14.944	35.695	24.516	1.00	66.93	C
ATOM	906	OE1	GLN	C	16	15.940	36.389	24.719	1.00	68.97	C
ATOM	907	NE2	GLN	C	16	14.657	34.621	25.244	1.00	66.55	C
ATOM	908	C	GLN	C	16	11.157	36.605	22.317	1.00	67.53	C
ATOM	909	O	GLN	C	16	11.172	37.836	22.397	1.00	68.90	C
ATOM	910	N	LYS	C	17	10.886	35.952	21.193	1.00	67.63	C
ATOM	911	CA	LYS	C	17	10.566	36.648	19.954	1.00	67.83	C
ATOM	912	CB	LYS	C	17	10.355	35.627	18.833	1.00	69.39	C
ATOM	913	CG	LYS	C	17	9.747	36.199	17.556	1.00	72.05	C
ATOM	914	CD	LYS	C	17	10.657	37.203	16.835	1.00	73.47	C
ATOM	915	CE	LYS	C	17	9.946	37.784	15.613	1.00	74.71	C
ATOM	916	NZ	LYS	C	17	10.885	38.603	14.795	1.00	76.15	C
ATOM	917	C	LYS	C	17	9.306	37.492	20.123	1.00	66.64	C
ATOM	918	O	LYS	C	17	9.244	38.632	19.652	1.00	67.45	C
ATOM	919	N	LYS	C	18	8.300	36.924	20.784	1.00	64.29	C
ATOM	920	CA	LYS	C	18	7.049	37.641	21.019	1.00	63.62	C
ATOM	921	CB	LYS	C	18	5.979	36.719	21.627	1.00	64.15	C
ATOM	922	CG	LYS	C	18	5.088	36.062	20.586	1.00	66.52	C
ATOM	923	CD	LYS	C	18	3.935	35.297	21.220	1.00	68.98	C
ATOM	924	CE	LYS	C	18	4.427	34.076	21.970	1.00	70.96	C
ATOM	925	NZ	LYS	C	18	5.098	33.116	21.040	1.00	72.62	C
ATOM	926	C	LYS	C	18	7.265	38.852	21.922	1.00	61.00	C
ATOM	927	O	LYS	C	18	6.854	39.958	21.585	1.00	61.84	C
ATOM	928	N	ILE	C	19	7.904	38.653	23.067	1.00	56.58	C
ATOM	929	CA	ILE	C	19	8.179	39.765	23.961	1.00	53.92	C
ATOM	930	CB	ILE	C	19	9.101	39.329	25.119	1.00	52.10	C
ATOM	931	CG2	ILE	C	19	9.719	40.545	25.799	1.00	51.95	C
ATOM	932	CG1	ILE	C	19	8.304	38.463	26.095	1.00	51.65	C
ATOM	933	CD1	ILE	C	19	9.103	37.908	27.247	1.00	50.93	C
ATOM	934	C	ILE	C	19	8.333	40.893	23.165	1.00	53.24	C
ATOM	935	O	ILE	C	19	8.604	42.069	23.438	1.00	52.35	C
ATOM	936	N	GLU	C	20	9.642	40.534	22.173	1.00	53.82	C
ATOM	937	CA	GLU	C	20	10.294	41.536	21.338	1.00	54.86	C
ATOM	938	CB	GLU	C	20	11.393	40.910	20.472	1.00	55.74	C
ATOM	939	CG	GLU	C	20	12.554	40.318	21.251	1.00	56.50	C
ATOM	940	CD	GLU	C	20	13.683	39.851	20.352	1.00	56.98	C
ATOM	941	OE1	GLU	C	20	13.473	38.918	19.543	1.00	56.87	C
ATOM	942	OE2	GLU	C	20	14.786	40.427	20.453	1.00	58.79	C
ATOM	943	C	GLU	C	20	9.245	42.188	20.437	1.00	55.80	C
ATOM	944	O	GLU	C	20	9.311	43.382	20.166	1.00	55.44	C
ATOM	945	N	ASN	C	21	8.289	41.389	19.972	1.00	55.46	C
ATOM	946	CA	ASN	C	21	7.223	41.899	19.118	1.00	57.62	C
ATOM	947	CB	ASN	C	21	6.392	40.754	18.530	1.00	59.92	C
ATOM	948	CG	ASN	C	21	7.060	40.101	17.325	1.00	63.29	C
ATOM	949	OD1	ASN	C	21	6.574	39.092	16.806	1.00	62.67	C
ATOM	950	ND2	ASN	C	21	8.169	40.684	16.866	1.00	61.87	C
ATOM	951	C	ASN	C	21	6.307	42.829	19.891	1.00	58.25	C

Figure 11P

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ATOM    952  O   ASN C  21       5.649  43.697  19.309  1.00 59.75      C
ATOM    953  N   GLU C  22       6.255  42.645  21.206  1.00 56.32      C
ATOM    954  CA  GLU C  22       5.411  43.489  22.030  1.00 53.64      C
ATOM    955  CB  GLU C  22       5.014  42.756  23.313  1.00 55.42      C
ATOM    956  CG  GLU C  22       3.786  43.357  23.967  1.00 60.12      C
ATOM    957  CD  GLU C  22       2.506  43.082  23.188  1.00 61.82      C
ATOM    958  OE1 GLU C  22       2.559  43.024  21.942  1.00 62.49      C
ATOM    959  OE2 GLU C  22       1.435  42.954  23.825  1.00 63.39      C
ATOM    960  C   GLU C  22       6.158  44.791  22.344  1.00 50.89      C
ATOM    961  O   GLU C  22       5.573  45.873  22.282  1.00 49.72      C
ATOM    962  N   ILE C  23       7.448  44.691  22.665  1.00 47.08      C
ATOM    963  CA  ILE C  23       8.259  45.876  22.948  1.00 46.40      C
ATOM    964  CB  ILE C  23       9.752  45.504  23.290  1.00 47.53      C
ATOM    965  CG2 ILE C  23      10.707  46.653  22.910  1.00 44.86      C
ATOM    966  CG1 ILE C  23       9.898  45.178  24.783  1.00 45.28      C
ATOM    967  CD1 ILE C  23       9.101  44.004  25.256  1.00 45.91      C
ATOM    968  C   ILE C  23       8.222  46.771  21.717  1.00 46.76      C
ATOM    969  O   ILE C  23       8.317  47.999  21.822  1.00 46.87      C
ATOM    970  N   ALA C  24       8.071  46.137  20.556  1.00 47.50      C
ATOM    971  CA  ALA C  24       8.002  46.828  19.271  1.00 46.10      C
ATOM    972  CB  ALA C  24       8.112  45.809  18.126  1.00 44.51      C
ATOM    973  C   ALA C  24       6.706  47.644  19.137  1.00 45.09      C
ATOM    974  O   ALA C  24       6.741  48.810  18.752  1.00 43.05      C
ATOM    975  N   ARG C  25       5.566  47.034  19.445  1.00 43.64      C
ATOM    976  CA  ARG C  25       4.301  47.753  19.346  1.00 45.79      C
ATOM    977  CB  ARG C  25       3.115  46.807  19.581  1.00 44.07      C
ATOM    978  CG  ARG C  25       3.045  45.680  18.564  1.00 48.16      C
ATOM    979  CD  ARG C  25       1.677  44.986  18.456  1.00 50.13      C
ATOM    980  NE  ARG C  25       1.216  44.299  19.664  1.00 54.12      C
ATOM    981  CZ  ARG C  25       0.665  44.888  20.725  1.00 58.36      C
ATOM    982  NH1 ARG C  25       0.475  46.206  20.756  1.00 59.26      C
ATOM    983  NH2 ARG C  25       0.268  44.148  21.755  1.00 59.83      C
ATOM    984  C   ARG C  25       4.257  48.908  20.345  1.00 47.24      C
ATOM    985  O   ARG C  25       3.941  50.038  19.978  1.00 50.68      C
ATOM    986  N   ILE C  26       4.584  48.617  21.601  1.00 47.54      C
ATOM    987  CA  ILE C  26       4.591  49.608  22.673  1.00 44.40      C
ATOM    988  CB  ILE C  26       5.042  48.959  24.001  1.00 43.91      C
ATOM    989  CG2 ILE C  26       5.259  50.026  25.071  1.00 45.47      C
ATOM    990  CG1 ILE C  26       4.010  47.930  24.450  1.00 42.59      C
ATOM    991  CD1 ILE C  26       4.445  47.138  25.663  1.00 40.19      C
ATOM    992  C   ILE C  26       5.532  50.766  22.379  1.00 44.58      C
ATOM    993  O   ILE C  26       5.193  51.935  22.564  1.00 42.04      C
ATOM    994  N   LYS C  27       6.721  50.422  21.919  1.00 46.75      C
ATOM    995  CA  LYS C  27       7.754  51.394  21.619  1.00 51.78      C
ATOM    996  CB  LYS C  27       8.915  50.674  20.951  1.00 54.23      C
ATOM    997  CG  LYS C  27      10.184  51.465  20.863  1.00 57.21      C
ATOM    998  CD  LYS C  27      11.313  50.479  20.644  1.00 60.99      C
ATOM    999  CE  LYS C  27      12.660  51.064  21.014  1.00 62.83      C
ATOM   1000  NZ  LYS C  27      13.750  50.060  20.828  1.00 64.49      C
ATOM   1001  C   LYS C  27       7.299  52.556  20.750  1.00 52.44      C
ATOM   1002  O   LYS C  27       7.334  53.710  21.165  1.00 54.11      C
ATOM   1003  N   LYS C  28       6.877  52.239  19.538  1.00 53.88      C
ATOM   1004  CA  LYS C  28       6.435  53.250  18.599  1.00 55.29      C
ATOM   1005  CB  LYS C  28       6.169  52.582  17.249  1.00 57.59      C
ATOM   1006  CG  LYS C  28       7.390  51.841  16.717  1.00 59.15      C
ATOM   1007  CD  LYS C  28       7.041  50.830  15.635  1.00 62.19      C
ATOM   1008  CE  LYS C  28       8.292  50.088  15.158  1.00 63.12      C
ATOM   1009  NZ  LYS C  28       9.029  49.411  16.282  1.00 65.69      C
ATOM   1010  C   LYS C  28       5.187  53.931  19.122  1.00 55.14      C
ATOM   1011  O   LYS C  28       5.052  55.147  19.030  1.00 57.43      C
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Figure 11Q

ATOM	1012	N	LEU	C	29	4.275	53.138	19.671	1.00	52.27	C
ATOM	1013	CA	LEU	C	29	3.025	53.649	20.214	1.00	51.04	C
ATOM	1014	CB	LEU	C	29	2.281	52.485	20.855	1.00	51.13	C
ATOM	1015	CG	LEU	C	29	0.776	52.493	21.051	1.00	50.66	C
ATOM	1016	CD1	LEU	C	29	0.051	52.868	19.755	1.00	51.59	C
ATOM	1017	CD2	LEU	C	29	0.389	51.100	21.491	1.00	50.29	C
ATOM	1018	C	LEU	C	29	3.347	54.739	21.245	1.00	50.83	C
ATOM	1019	O	LEU	C	29	2.739	55.805	21.269	1.00	53.58	C
ATOM	1020	N	LEU	C	30	4.327	54.457	22.089	1.00	50.52	C
ATOM	1021	CA	LEU	C	30	4.767	55.397	23.100	1.00	48.88	C
ATOM	1022	CB	LEU	C	30	5.813	54.730	23.997	1.00	48.03	C
ATOM	1023	CG	LEU	C	30	6.485	55.530	25.113	1.00	47.31	C
ATOM	1024	CD1	LEU	C	30	5.447	56.172	26.033	1.00	45.24	C
ATOM	1025	CD2	LEU	C	30	7.398	54.575	25.889	1.00	48.28	C
ATOM	1026	C	LEU	C	30	5.374	56.587	22.379	1.00	48.83	C
ATOM	1027	O	LEU	C	30	5.020	57.736	22.642	1.00	48.40	C
ATOM	1028	N	GLN	C	31	6.298	56.289	21.470	1.00	49.93	C
ATOM	1029	CA	GLN	C	31	6.983	57.304	20.670	1.00	52.00	C
ATOM	1030	CB	GLN	C	31	7.822	56.609	19.590	1.00	55.56	C
ATOM	1031	CG	GLN	C	31	8.628	57.513	18.645	1.00	61.26	C
ATOM	1032	CD	GLN	C	31	9.768	58.241	19.333	1.00	64.58	C
ATOM	1033	OE1	GLN	C	31	10.233	57.818	20.391	1.00	68.00	C
ATOM	1034	NE2	GLN	C	31	10.249	59.318	18.715	1.00	64.37	C
ATOM	1035	C	GLN	C	31	5.947	58.225	20.009	1.00	49.56	C
ATOM	1036	O	GLN	C	31	6.192	59.415	19.814	1.00	45.68	C
ATOM	1037	N	LEU	C	32	4.793	57.657	19.675	1.00	47.64	C
ATOM	1038	CA	LEU	C	32	3.723	58.401	19.034	1.00	48.95	C
ATOM	1039	CB	LEU	C	32	2.689	57.433	18.461	1.00	50.72	C
ATOM	1040	CG	LEU	C	32	1.602	57.935	17.502	1.00	51.93	C
ATOM	1041	CD1	LEU	C	32	2.209	58.293	16.154	1.00	50.26	C
ATOM	1042	CD2	LEU	C	32	0.554	56.840	17.313	1.00	51.55	C
ATOM	1043	C	LEU	C	32	3.070	59.295	20.077	1.00	49.32	C
ATOM	1044	O	LEU	C	32	3.040	60.519	19.929	1.00	50.01	C
ATOM	1045	N	THR	C	33	2.545	58.659	21.125	1.00	48.74	C
ATOM	1046	CA	THR	C	33	1.878	59.324	22.246	1.00	43.86	C
ATOM	1047	CB	THR	C	33	1.643	58.329	23.400	1.00	46.04	C
ATOM	1048	OG1	THR	C	33	0.707	57.332	22.977	1.00	47.18	C
ATOM	1049	CG2	THR	C	33	1.121	59.039	24.639	1.00	42.89	C
ATOM	1050	C	THR	C	33	2.683	60.494	22.771	1.00	41.04	C
ATOM	1051	O	THR	C	33	2.132	61.537	23.122	1.00	39.26	C
ATOM	1052	N	VAL	C	34	3.992	60.303	22.843	1.00	38.83	C
ATOM	1053	CA	VAL	C	34	4.886	61.346	23.301	1.00	36.90	C
ATOM	1054	CB	VAL	C	34	6.329	60.825	23.377	1.00	33.71	C
ATOM	1055	CG1	VAL	C	34	7.270	61.907	23.904	1.00	29.40	C
ATOM	1056	CG2	VAL	C	34	6.366	59.590	24.251	1.00	31.78	C
ATOM	1057	C	VAL	C	34	4.795	62.437	22.254	1.00	38.65	C
ATOM	1058	O	VAL	C	34	4.489	63.595	22.556	1.00	39.38	C
ATOM	1059	N	TRP	C	35	5.049	62.038	21.010	1.00	42.18	C
ATOM	1060	CA	TRP	C	35	5.002	62.927	19.868	1.00	40.00	C
ATOM	1061	CB	TRP	C	35	4.991	62.134	18.563	1.00	40.06	C
ATOM	1062	CG	TRP	C	35	4.848	63.020	17.399	1.00	36.56	C
ATOM	1063	CD2	TRP	C	35	3.696	63.161	16.561	1.00	36.91	C
ATOM	1064	CE2	TRP	C	35	3.968	64.212	15.673	1.00	41.20	C
ATOM	1065	CE3	TRP	C	35	2.457	62.505	16.503	1.00	40.31	C
ATOM	1066	CD1	TRP	C	35	5.748	63.944	16.974	1.00	35.30	C
ATOM	1067	NE1	TRP	C	35	5.228	64.673	15.945	1.00	39.45	C
ATOM	1068	CZ2	TRP	C	35	3.037	64.643	14.704	1.00	38.75	C
ATOM	1069	CZ3	TRP	C	35	1.528	62.934	15.541	1.00	39.54	C
ATOM	1070	CH2	TRP	C	35	1.827	63.984	14.651	1.00	41.30	C
ATOM	1071	C	TRP	C	35	3.764	63.833	19.901	1.00	39.80	C

Figure 11R

ATOM	1072	O	TRP	C	35	3.868	65.052	19.769	1.00	38.39	C
ATOM	1073	N	GLY	C	36	2.601	63.210	20.059	1.00	36.88	C
ATOM	1074	CA	GLY	C	36	1.356	63.957	20.103	1.00	38.94	C
ATOM	1075	C	GLY	C	36	1.315	64.973	21.226	1.00	38.45	C
ATOM	1076	O	GLY	C	36	0.931	66.114	21.001	1.00	37.76	C
ATOM	1077	N	ILE	C	37	1.700	64.557	22.435	1.00	40.86	C
ATOM	1078	CA	ILE	C	37	1.724	65.442	23.604	1.00	36.66	C
ATOM	1079	CB	ILE	C	37	2.352	64.758	24.857	1.00	36.83	C
ATOM	1080	CG2	ILE	C	37	2.489	65.766	26.005	1.00	27.32	C
ATOM	1081	CG1	ILE	C	37	1.512	63.548	25.275	1.00	37.14	C
ATOM	1082	CD1	ILE	C	37	2.066	62.794	26.501	1.00	35.85	C
ATOM	1083	C	ILE	C	37	2.587	66.655	23.284	1.00	38.37	C
ATOM	1084	O	ILE	C	37	2.187	67.788	23.529	1.00	37.68	C
ATOM	1085	N	LYS	C	38	3.775	66.399	22.740	1.00	40.28	C
ATOM	1086	CA	LYS	C	38	4.717	67.456	22.381	1.00	42.51	C
ATOM	1087	CB	LYS	C	38	5.927	66.868	21.629	1.00	46.36	C
ATOM	1088	CG	LYS	C	38	7.109	67.829	21.391	1.00	52.00	C
ATOM	1089	CD	LYS	C	38	8.125	67.162	20.433	1.00	56.10	C
ATOM	1090	CE	LYS	C	38	9.365	68.008	20.096	1.00	56.61	C
ATOM	1091	NZ	LYS	C	38	10.340	68.155	21.222	1.00	59.57	C
ATOM	1092	C	LYS	C	38	3.995	68.445	21.483	1.00	42.06	C
ATOM	1093	O	LYS	C	38	4.351	69.629	21.428	1.00	41.76	C
ATOM	1094	N	GLN	C	39	2.977	67.966	20.774	1.00	39.73	C
ATOM	1095	CA	GLN	C	39	2.232	68.862	19.908	1.00	40.05	C
ATOM	1096	CB	GLN	C	39	1.499	68.100	18.778	1.00	41.27	C
ATOM	1097	CG	GLN	C	39	2.385	67.148	17.928	1.00	42.44	C
ATOM	1098	CD	GLN	C	39	3.681	67.786	17.465	1.00	42.00	C
ATOM	1099	OE1	GLN	C	39	3.678	68.822	16.813	1.00	44.81	C
ATOM	1100	NE2	GLN	C	39	4.802	67.163	17.802	1.00	46.04	C
ATOM	1101	C	GLN	C	39	1.241	69.638	20.781	1.00	36.22	C
ATOM	1102	O	GLN	C	39	1.344	70.845	20.885	1.00	34.78	C
ATOM	1103	N	LEU	C	40	0.285	68.950	21.398	1.00	34.58	C
ATOM	1104	CA	LEU	C	40	-0.696	69.625	22.268	1.00	36.22	C
ATOM	1105	CB	LEU	C	40	-1.465	68.595	23.096	1.00	34.67	C
ATOM	1106	CG	LEU	C	40	-2.365	69.192	24.186	1.00	34.61	C
ATOM	1107	CD1	LEU	C	40	-3.392	70.142	23.510	1.00	34.28	C
ATOM	1108	CD2	LEU	C	40	-3.057	68.084	24.972	1.00	30.45	C
ATOM	1109	C	LEU	C	40	-0.029	70.630	23.226	1.00	36.51	C
ATOM	1110	O	LEU	C	40	-0.494	71.755	23.419	1.00	36.17	C
ATOM	1111	N	GLN	C	41	1.068	70.220	23.832	1.00	36.56	C
ATOM	1112	CA	GLN	C	41	1.764	71.106	24.751	1.00	38.77	C
ATOM	1113	CB	GLN	C	41	2.883	70.310	25.433	1.00	38.66	C
ATOM	1114	CG	GLN	C	41	3.606	70.994	26.582	1.00	46.41	C
ATOM	1115	CD	GLN	C	41	4.245	69.979	27.529	1.00	50.25	C
ATOM	1116	OE1	GLN	C	41	4.898	69.028	27.091	1.00	53.94	C
ATOM	1117	NE2	GLN	C	41	4.063	70.180	28.831	1.00	52.04	C
ATOM	1118	C	GLN	C	41	2.291	72.336	23.998	1.00	37.58	C
ATOM	1119	O	GLN	C	41	2.190	73.466	24.486	1.00	38.73	C
ATOM	1120	N	ALA	C	42	2.827	72.128	22.795	1.00	36.75	C
ATOM	1121	CA	ALA	C	42	3.365	73.249	22.014	1.00	36.93	C
ATOM	1122	CB	ALA	C	42	4.084	72.717	20.779	1.00	32.48	C
ATOM	1123	C	ALA	C	42	2.241	74.209	21.600	1.00	35.85	C
ATOM	1124	O	ALA	C	42	2.407	75.427	21.602	1.00	34.18	C
ATOM	1125	N	ARG	C	43	1.101	73.629	21.249	1.00	32.51	C
ATOM	1126	CA	ARG	C	43	-0.072	74.365	20.829	1.00	34.59	C
ATOM	1127	CB	ARG	C	43	-1.152	73.357	20.524	1.00	34.80	C
ATOM	1128	CG	ARG	C	43	-2.467	73.891	20.060	1.00	36.54	C
ATOM	1129	CD	ARG	C	43	-3.310	72.667	19.769	1.00	37.93	C
ATOM	1130	NE	ARG	C	43	-4.631	72.945	19.236	1.00	40.51	C
ATOM	1131	CZ	ARG	C	43	-5.481	71.985	18.901	1.00	42.74	C

Figure 11S

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ATOM   1132  NH1 ARG C  43      -5.127  70.717  19.051  1.00 41.40      C
ATOM   1133  NH2 ARG C  43      -6.676  72.288  18.421  1.00 44.00      C
ATOM   1134  C   ARG C  43      -0.568  75.347  21.883  1.00 37.96      C
ATOM   1135  O   ARG C  43      -1.049  76.425  21.558  1.00 36.78      C
ATOM   1136  N   ILE C  44      -0.434  74.971  23.151  1.00 41.66      C
ATOM   1137  CA  ILE C  44      -0.901  75.799  24.250  1.00 43.04      C
ATOM   1138  CB  ILE C  44      -1.403  74.891  25.390  1.00 45.88      C
ATOM   1139  CG2 ILE C  44      -1.802  75.717  26.594  1.00 46.21      C
ATOM   1140  CG1 ILE C  44      -2.572  74.041  24.876  1.00 46.16      C
ATOM   1141  CD1 ILE C  44      -2.926  72.877  25.786  1.00 50.31      C
ATOM   1142  C   ILE C  44       0.109  76.802  24.807  1.00 41.15      C
ATOM   1143  O   ILE C  44      -0.235  77.961  25.047  1.00 40.03      C
ATOM   1144  N   LEU C  45       1.345  76.350  25.005  1.00 40.33      C
ATOM   1145  CA  LEU C  45       2.401  77.184  25.579  1.00 39.81      C
ATOM   1146  CB  LEU C  45       3.357  76.322  26.422  1.00 40.22      C
ATOM   1147  CG  LEU C  45       2.889  75.608  27.694  1.00 40.80      C
ATOM   1148  CD1 LEU C  45       1.733  74.714  27.364  1.00 42.51      C
ATOM   1149  CD2 LEU C  45       4.029  74.789  28.299  1.00 39.44      C
ATOM   1150  C   LEU C  45       3.215  77.953  24.540  1.00 38.95      C
ATOM   1151  O   LEU C  45       3.071  77.689  23.327  1.00 39.83      C
ATOM   1152  NT  LEU C  45       4.014  78.810  24.964  1.00 39.47      C
ATOM   1153  OH2 TIP W   2       8.280  62.369  27.138  1.00 38.82      W
ATOM   1154  OH2 TIP W   3      28.782  24.001  17.582  1.00 78.47      W
ATOM   1155  OH2 TIP W   4       0.492  62.209  33.896  1.00 50.43      W
ATOM   1156  OH2 TIP W   5       6.020  70.609  23.199  1.00 45.29      W
ATOM   1157  OH2 TIP W   6       1.993  78.695  31.896  1.00 37.25      W
ATOM   1158  OH2 TIP W   7      20.294  18.975  19.485  1.00 49.56      W
ATOM   1159  OH2 TIP W   8      18.592  15.442  35.405  1.00 34.86      W
ATOM   1160  OH2 TIP W   9      -5.907  64.337  32.524  1.00 31.24      W
ATOM   1161  OH2 TIP W  10      11.567  18.853  30.945  1.00 47.94      W
ATOM   1162  OH2 TIP W  11      -9.321  65.456  23.794  1.00 46.60      W
ATOM   1163  OH2 TIP W  12      -2.842  65.953  28.078  1.00 59.15      W
ATOM   1164  OH2 TIP W  13      -1.409  77.305  18.859  1.00 37.51      W
ATOM   1165  OH2 TIP W  14      -5.597  64.224  37.408  1.00 39.02      W
ATOM   1166  OH2 TIP W  15      -5.079  75.908  18.460  1.00 48.65      W
ATOM   1167  OH2 TIP W  16      12.444  58.431  21.920  1.00 62.97      W
ATOM   1168  OH2 TIP W  17     -12.927  70.555  24.520  1.00 61.81      W
ATOM   1169  OH2 TIP W  18      14.897  23.356  34.046  1.00 40.13      W
ATOM   1170  OH2 TIP W  19       3.154  40.721  28.964  1.00 29.89      W
ATOM   1171  OH2 TIP W  20       4.290  81.951  24.440  1.00 44.83      W
ATOM   1172  OH2 TIP W  21      26.490  23.104  32.265  1.00 62.67      W
ATOM   1173  OH2 TIP W  22      13.085  59.162  33.622  1.00 54.53      W
ATOM   1174  OH2 TIP W  23      -0.166  45.626  35.200  1.00 56.34      W
ATOM   1175  OH2 TIP W  24     -10.278  62.692  33.867  1.00 64.05      W
ATOM   1176  OH2 TIP W  25      22.697  10.892  29.710  1.00100.00      W
ATOM   1177  OH2 TIP W  26       4.281  39.194  26.136  1.00 62.29      W
ATOM   1178  OH2 TIP W  27      22.833  20.843  19.882  1.00 59.57      W
ATOM   1179  OH2 TIP W  28     -10.030  74.838  23.517  1.00 53.18      W
ATOM   1180  OH2 TIP W  29       1.246  80.456  24.973  1.00 36.18      W
ATOM   1181  OH2 TIP W  30      -3.034  76.181  17.506  1.00 50.44      W
ATOM   1182  OH2 TIP W  31       1.424  49.275  18.155  1.00 44.03      W
ATOM   1183  OH2 TIP W  32       6.269  64.921  23.710  1.00 31.68      W
ATOM   1184  OH2 TIP W  33      27.134  28.497  40.798  1.00 60.31      W
ATOM   1185  OH2 TIP W  34      24.326  28.221  42.517  1.00 85.52      W
ATOM   1186  OH2 TIP W  35      24.492  26.009  31.950  1.00 68.20      W
ATOM   1187  OH2 TIP W  36      17.270  23.540  41.621  1.00 45.61      W
ATOM   1188  OH2 TIP W  37      17.175  27.169  41.299  1.00 57.26      W
ATOM   1189  OH2 TIP W  38      17.133  30.154  42.769  1.00 94.65      W
ATOM   1190  OH2 TIP W  39      23.961  29.473  38.207  1.00 73.43      W
ATOM   1191  OH2 TIP W  40      26.646  30.299  35.030  1.00 86.46      W
```

Figure 11T

ATOM	1192	OH2	TIP	W	41	21.799	33.921	37.475	1.00	98.23	W
ATOM	1193	OH2	TIP	W	42	12.296	24.508	37.800	1.00	73.10	W
ATOM	1194	OH2	TIP	W	43	10.910	28.524	40.599	1.00	65.23	W
ATOM	1195	OH2	TIP	W	44	8.726	30.065	36.214	1.00	62.46	W
ATOM	1196	OH2	TIP	W	45	20.748	34.061	34.804	1.00	62.12	W
ATOM	1197	OH2	TIP	W	46	7.462	29.159	29.170	1.00	88.23	W
ATOM	1198	OH2	TIP	W	47	7.466	31.280	33.124	1.00	56.10	W
ATOM	1199	OH2	TIP	W	48	6.666	26.619	36.241	1.00	52.76	W
ATOM	1200	OH2	TIP	W	49	3.823	27.148	35.557	1.00	92.76	W
ATOM	1201	OH2	TIP	W	50	7.608	28.183	32.367	1.00	83.54	W
ATOM	1202	OH2	TIP	W	51	10.064	35.767	38.975	1.00	68.12	W
ATOM	1203	OH2	TIP	W	52	14.649	36.973	38.236	1.00	73.09	W
ATOM	1204	OH2	TIP	W	53	16.799	36.406	39.778	1.00	48.69	W
ATOM	1205	OH2	TIP	W	54	15.456	39.954	39.598	1.00	48.97	W
ATOM	1206	OH2	TIP	W	55	8.442	41.891	37.753	1.00	57.63	W
ATOM	1207	OH2	TIP	W	56	9.926	44.040	39.986	1.00	80.20	W
ATOM	1208	OH2	TIP	W	57	3.713	35.630	32.034	1.00	65.94	W
ATOM	1209	OH2	TIP	W	58	4.004	32.569	30.481	1.00	98.02	W
ATOM	1210	OH2	TIP	W	59	13.514	45.594	36.374	1.00	45.92	W
ATOM	1211	OH2	TIP	W	60	12.274	44.358	32.693	1.00	69.72	W
ATOM	1212	OH2	TIP	W	61	-1.770	41.459	30.288	1.00	86.62	W
ATOM	1213	OH2	TIP	W	62	-0.747	39.619	34.003	1.00	85.57	W
ATOM	1214	OH2	TIP	W	63	2.370	42.056	36.997	1.00	63.26	W
ATOM	1215	OH2	TIP	W	64	7.646	47.813	26.559	1.00	86.77	W
ATOM	1216	OH2	TIP	W	65	-1.942	50.096	25.818	1.00	33.47	W
ATOM	1217	OH2	TIP	W	66	-0.455	48.262	24.057	1.00	48.49	W
ATOM	1218	OH2	TIP	W	67	-1.850	44.976	32.352	1.00	46.88	W
ATOM	1219	OH2	TIP	W	68	-4.779	47.469	30.587	1.00	53.38	W
ATOM	1220	OH2	TIP	W	69	-8.800	47.417	33.155	1.00	55.34	W
ATOM	1221	OH2	TIP	W	70	-7.762	51.374	35.608	1.00	72.46	W
ATOM	1222	OH2	TIP	W	71	5.493	50.307	35.418	1.00	63.93	W
ATOM	1223	OH2	TIP	W	72	-2.293	60.557	33.176	1.00	58.13	W
ATOM	1224	OH2	TIP	W	73	-3.891	59.956	22.859	1.00	42.99	W
ATOM	1225	OH2	TIP	W	74	-2.324	52.365	23.808	1.00	68.12	W
ATOM	1226	OH2	TIP	W	75	-4.610	53.603	23.534	1.00	99.86	W
ATOM	1227	OH2	TIP	W	76	-5.369	51.351	24.806	1.00	66.59	W
ATOM	1228	OH2	TIP	W	77	-9.158	53.927	27.711	1.00	59.38	W
ATOM	1229	OH2	TIP	W	78	-6.839	60.379	22.155	1.00	48.43	W
ATOM	1230	OH2	TIP	W	79	-7.811	55.209	31.835	1.00	63.25	W
ATOM	1231	OH2	TIP	W	80	-8.988	55.740	34.680	1.00	48.03	W
ATOM	1232	OH2	TIP	W	81	-14.358	62.793	31.478	1.00	77.34	W
ATOM	1233	OH2	TIP	W	82	-14.884	67.194	30.264	1.00	100.00	W
ATOM	1234	OH2	TIP	W	83	-13.964	62.903	27.850	1.00	61.59	W
ATOM	1235	OH2	TIP	W	84	-16.467	64.338	27.598	1.00	62.99	W
ATOM	1236	OH2	TIP	W	85	-14.165	71.419	31.235	1.00	58.55	W
ATOM	1237	OH2	TIP	W	86	-12.150	75.052	20.683	1.00	54.74	W
ATOM	1238	OH2	TIP	W	87	-15.348	66.527	23.972	1.00	86.65	W
ATOM	1239	OH2	TIP	W	88	23.657	18.784	16.110	1.00	46.11	W
ATOM	1240	OH2	TIP	W	89	21.774	13.448	17.383	1.00	55.62	W
ATOM	1241	OH2	TIP	W	90	28.955	20.801	18.398	1.00	47.29	W
ATOM	1242	OH2	TIP	W	91	19.043	22.428	18.931	1.00	70.31	W
ATOM	1243	OH2	TIP	W	92	32.348	21.741	32.055	1.00	80.85	W
ATOM	1244	OH2	TIP	W	93	31.544	26.386	31.293	1.00	80.53	W
ATOM	1245	OH2	TIP	W	94	30.484	31.504	24.099	1.00	51.19	W
ATOM	1246	OH2	TIP	W	95	28.981	30.812	18.458	1.00	98.45	W
ATOM	1247	OH2	TIP	W	96	25.233	35.680	28.569	1.00	53.47	W
ATOM	1248	OH2	TIP	W	97	25.740	37.432	31.266	1.00	96.40	W
ATOM	1249	OH2	TIP	W	98	18.343	27.853	17.008	1.00	87.39	W
ATOM	1250	OH2	TIP	W	99	26.162	40.002	24.887	1.00	63.29	W
ATOM	1251	OH2	TIP	W	100	18.396	37.649	32.149	1.00	75.85	W

Figure 11U

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ATOM   1252  OH2 TIP W 101      20.897  31.301  18.264  1.00 88.40      W
ATOM   1253  OH2 TIP W 102      19.191  42.582  21.453  1.00 55.18      W
ATOM   1254  OH2 TIP W 103      23.958  41.188  26.907  1.00 78.30      W
ATOM   1255  OH2 TIP W 104      18.433  46.716  22.932  1.00 54.59      W
ATOM   1256  OH2 TIP W 105      22.353  48.547  25.042  1.00 59.94      W
ATOM   1257  OH2 TIP W 106      21.797  41.049  34.496  1.00 78.60      W
ATOM   1258  OH2 TIP W 107      21.437  46.210  33.535  1.00 75.53      W
ATOM   1259  OH2 TIP W 108      14.907  43.959  21.380  1.00 54.65      W
ATOM   1260  OH2 TIP W 109      15.635  42.456  19.119  1.00 58.03      W
ATOM   1261  OH2 TIP W 110      19.533  44.310  33.666  1.00 80.58      W
ATOM   1262  OH2 TIP W 111      18.747  50.736  29.399  1.00 60.97      W
ATOM   1263  OH2 TIP W 112      21.131  52.757  28.680  1.00 55.70      W
ATOM   1264  OH2 TIP W 113      17.303  55.311  38.133  1.00 72.59      W
ATOM   1265  OH2 TIP W 114      18.939  58.215  28.845  1.00 79.75      W
ATOM   1266  OH2 TIP W 115      14.666  59.680  28.964  1.00 50.64      W
ATOM   1267  OH2 TIP W 116      17.408  62.649  28.523  1.00 74.43      W
ATOM   1268  OH2 TIP W 117      12.106  61.533  23.810  1.00 89.64      W
ATOM   1269  OH2 TIP W 118      10.138  60.131  37.626  1.00 89.60      W
ATOM   1270  OH2 TIP W 119      14.125  60.999  36.831  1.00 78.03      W
ATOM   1271  OH2 TIP W 120       6.987  65.584  27.400  1.00 63.28      W
ATOM   1272  OH2 TIP W 121       8.699  65.761  30.950  1.00 64.96      W
ATOM   1273  OH2 TIP W 122      11.912  66.582  33.458  1.00 45.24      W
ATOM   1274  OH2 TIP W 123       7.712  69.520  31.053  1.00 89.81      W
ATOM   1275  OH2 TIP W 124       0.300  66.328  28.053  1.00 83.63      W
ATOM   1276  OH2 TIP W 125      18.739  12.093  36.575  1.00 68.16      W
ATOM   1277  OH2 TIP W 126       8.341  17.901  23.874  1.00 69.12      W
ATOM   1278  OH2 TIP W 127       6.665  20.667  30.766  1.00 79.31      W
ATOM   1279  OH2 TIP W 128      13.178  21.216  32.239  1.00 55.97      W
ATOM   1280  OH2 TIP W 129       7.700  21.187  21.255  1.00 66.56      W
ATOM   1281  OH2 TIP W 130      17.038  26.024  19.828  1.00 40.17      W
ATOM   1282  OH2 TIP W 131       9.682  31.384  16.376  1.00 77.12      W
ATOM   1283  OH2 TIP W 132      11.568  29.117  15.187  1.00 59.43      W
ATOM   1284  OH2 TIP W 133       2.602  30.287  27.387  1.00 64.52      W
ATOM   1285  OH2 TIP W 134      10.743  41.812  16.813  1.00 84.35      W
ATOM   1286  OH2 TIP W 135      13.070  38.706  12.664  1.00 61.24      W
ATOM   1287  OH2 TIP W 136       9.262  44.518  14.939  1.00 51.92      W
ATOM   1288  OH2 TIP W 137      12.139  53.137  17.554  1.00 56.22      W
ATOM   1289  OH2 TIP W 138      14.403  57.453  15.838  1.00 66.72      W
ATOM   1290  OH2 TIP W 139      11.017  71.423  23.035  1.00 71.76      W
ATOM   1291  OH2 TIP W 140      10.451  75.718  24.795  1.00 58.85      W
ATOM   1292  OH2 TIP W 141      11.223  65.048  21.172  1.00 84.46      W
ATOM   1293  OH2 TIP W 142       8.196  70.691  21.387  1.00 66.14      W
ATOM   1294  OH2 TIP W 143       3.381  51.168  17.717  1.00 51.91      W
ATOM   1295  OH2 TIP W 144      13.735  48.059  19.325  1.00 73.18      W
ATOM   1296  OH2 TIP W 145       2.524  42.027  17.393  1.00 80.66      W
ATOM   1297  OH2 TIP W 146       2.024  39.150  18.549  1.00 74.07      W
ATOM   1298  OH2 TIP W 147       0.486  41.584  19.991  1.00 97.41      W
ATOM   1299  OH2 TIP W 148       0.060  40.945  24.577  1.00 78.10      W
ATOM   1300  OH2 TIP W 149      14.261  36.624  16.034  1.00 71.76      W
ATOM   1301  OH2 TIP W 150      17.041  33.288  18.134  1.00 55.41      W
ATOM   1302  OH2 TIP W 151      12.012  53.850  23.650  1.00 34.32      W
ATOM   1303  OH2 TIP W 152       0.421  41.869  28.444  1.00 53.88      W
ATOM   1304 CL-1 CL  I   1      13.184  36.734  27.569  1.00 62.34      I
END
```

Figure 11V

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/ 17351

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 40 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 99/17351

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/16 A61K38/10 A61K38/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.K. JUDICE ET AL.: "Inhibition of HIV type 1 infectivity by constrained alpha-helical peptides: Implications for the viral fusion mechanism" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, December 1997 (1997-12), pages 13426-13430, XP002126803 WASHINGTON US page 13428, right-hand column, paragraph 1 -page 13429, right-hand column, paragraph 1; figure 1 --- -/--	1,74-87

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

³ Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 December 1999	18/01/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 99/17351

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